Synthesis of novel C2 symmetric ketene equivalents for asymmetric Diels-Alder reactions

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SYNTHESIS OF NOVEL C_2 SYMMETRIC KETENE EQUIVALENTS FOR ASYMMETRIC DIELS-ALDER REACTIONS.

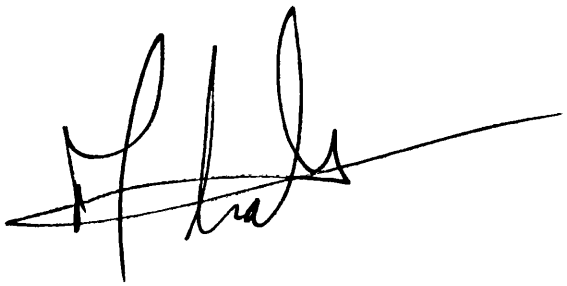
Submitted by

Mark Lightowler

For the degree of Ph.D.

Of the University of Bath

1993



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"If not you, who?

If not now, when?"

Dedicated to those in pursuit of their dreams.

ACKNOWLEDGEMENTS

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ABSTRACT

Cyclic and bicyclic ketones are important intermediates in organic synthesis. Cycloaddition of a 1,4 diene with ketene affords cyclobutanones *via* a [2+2] reaction. Chapter one reviews the design of ketene equivalents which undergo [4+2] cycloadditions instead. The origins of stereoselectivity for each type of ketene equivalent are discussed.

Our approach to the synthesis of a novel type of ketene equivalent are outlined in chapter two. Starting form anthranilic acid a C_2 symmetric cyclic dienophile was synthesised by selective *trans* sulphoxidation, Mannich reaction, and elimination to afford (1RS,3RS)-2-methylene -1,3-benzodithiole-1,3-dioxide. Dithiane and dithiolane derived *trans* dioxide ketene equivalents were synthesised from the five and six membered ethylesters by reduction, *trans* sulphoxidation and dehydration.

The Diels-Alder reaction of the three dienophiles with cyclic and acyclic dienes was investigated and the conditions that gave Diels-Alder adducts in high diastereomeric excess were determined. The nature of the stereoselectivity was investigated and found to be due to preferential approach of the diene over the sulphur lone pair rather than over the sulphinyl oxygen. Hydrolysis of the Diels-Alder adducts yielded norborneneone. The attempted synthesis of homocarbovir is outlined in chapter four. This involved a palladium (0) catalysed coupling of an N-heterocycle with a lactone derived from norborneneone.

Full experimental details for the preparation of these compounds is given in chapter five.

ABBREVIATIONS

Ac	Acetyl
Ant	Anthracene
aq	Aqueous
Bu	Butyl
^{n}BuLi	^{n}Butyllithium
^{t}Bu	*tert*-Butyl
C.I.	Chemical ionisation
cmc mpt	cyclohexyl-morpholinoethyl-carbodiimide metho-p-toluene sulphonate.
*m*CPBA	*meta*-Chloroperoxybenzoic acid
2D COSY	two dimensional correlated spectroscopy
Cp	cyclopentadiene
Cy	cyclohexyl
DBU	1,8-Diazabicyclo[5.4.0] undec-7-ene
DEAD	Diethylazodicarboxylate
DE	Diastereomeric excess
DIAD	Diisopropylazodicarboxylate
DMAP	Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulphoxide
DSC	Disuccinamdyl carbonate
EE	Enantiomeric excess
E.I.	Electron ionisation
Et	Ethyl
HOMO	Highest occupied molecular orbital

Hr	Hour
IR	Infrared
J	coupling constant
KHMDS	Potassium hexamethyldisilazide
LAH	Lithium aluminium hydride
LDA	Lithium Diisopropylamide
LUMO	Lowest unoccupied molecular orbital
Me	Methyl
min	minute
m.p.	melting point
Nap	Napthalene
n.m.r.	nuclear magnetic resonance
nOe	nuclear Overhauser effect
p.p.m.	parts per million
Pr	propyl
*i*Pr	*iso*-propyl
py	pyridine
rt	room temperature
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilane
Tol	Toluene

CONTENTS

Chapter Two: Results and discussion 1.

Appendicies

CHAPTER ONE

INTRODUCTION

KETENE EQUIVALENTS

Chapter 1

1.0 INTRODUCTION

The Diels-Alder cycloaddition since its first report by Otto Diels and Kurt Alder[1] has emerged as one of the most efficient methods in organic synthesis not only in terms of carbon-carbon bond formation[2] but also for the synthesis of intermediates with a high degree of functionality.[3]

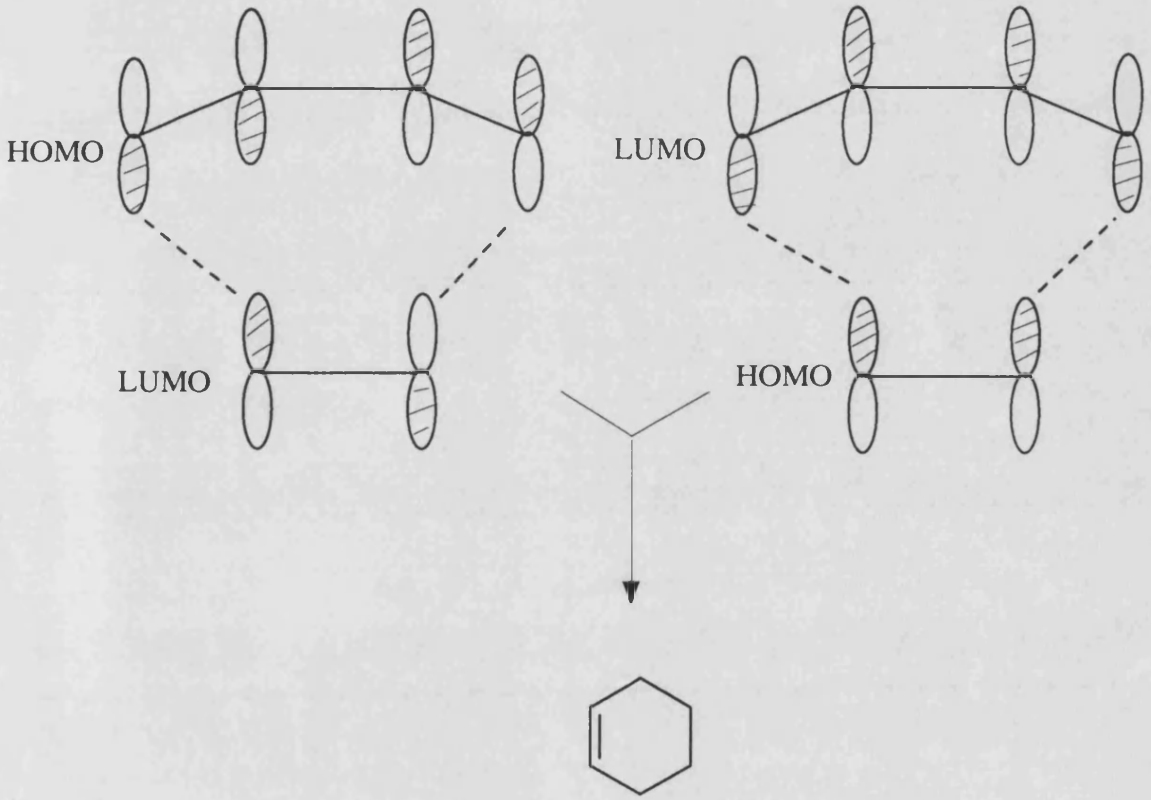
Since this first publication the [4+2] cycloaddition was followed by [2+1], [2+2], [3+2] as well as 1,3 dipolar cycloadditions[4]. This thesis is primarily concerned with [4+2] cycloadditions of synthetic equivalents of ketene. As ketene itself undergoes a formal [2+2] cycloaddition with 1,4 dienes affording cyclobutanones[5], it is pertinent to describe the salient features of the Diels-Alder reaction as well as the [2+2] cycloaddition where they correspond to the design of ketene equivalents.

1.1 The Diels-Alder Reaction

Much literature has been published on the Diels-Alder reaction.[6-7] In general it may be described as the addition of a double bond to a 1,4 conjugated diene affording a six membered ring in which four stereocentres may be simultaneously generated. The term [4+2] associated with the Diels-Alder reaction denotes were new bonds are formed (in this case between carbon four of the dienophile and carbon two of the diene), by implication a six membered ring is formed. [4+2] Cycloadditions have been named after their discoverers, the term Diels-Alder reaction and [4+2] cycloaddition are used interchangeably.

The cycloaddition of a diene and dienophile may best be described by the overlap of molecular orbitals as shown in **fig 1.1**. The simplest case, reaction of ethylene and butadiene is shown.

Fig 1.1



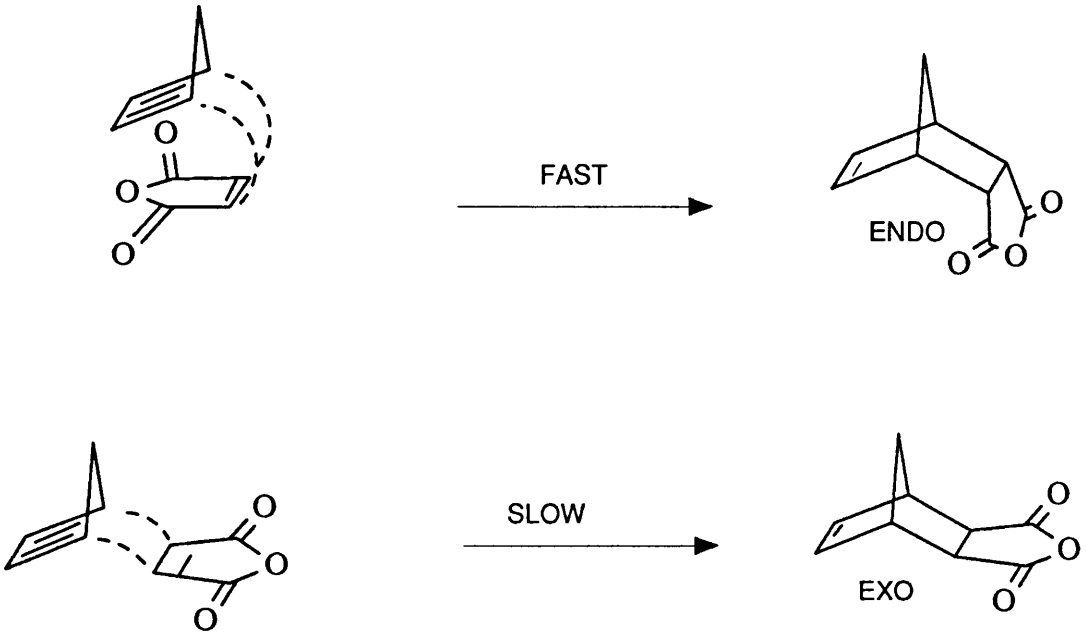
Each component of the cycloaddition has a set of orbitals, highest occupied molecular orbital (HOMO), and the lowest unoccupied molecular orbital, (LUMO)[6]. Allowed cycloadditions requires overlap of a HOMO of one component with the LUMO of the second component. It is the interaction between the HOMO and LUMO orbitals which determine the rate of cycloaddition, the smaller the energy separation between the two sets of orbitals the faster the reaction. To minimise this difference in

energy between the HOMO and the LUMO requires that one compound will be electron rich (normally the diene) and the other component (the dienophile) would be electron deficient. There are many examples of an electron deficient dienes and electron rich dienophiles and this type of cycloaddition reaction is known as inverse electron demand Diels-Alder.[8]

Mechanistically, Diels-Alder reactions are thought to proceed through a cyclic six centred transition state in a one step concerted fashion[9] i.e. with no intermediate formation. However alternative mechanisms have been postulated. The first invokes the formation of a diradical[10] in which the terminus of one side of the diene fastens to one terminus of the dienophile. In the second step the adjacent radicals combine to form the second bond. The final theory involves the movement of electron pairs in a stepwise fashion forming an intermediate betaine[11] followed by the formation of a second σ bond. Evidence for the concerted pathway is greater than that for the other two however they may still participate under certain conditions. The evidence for the concerted pathway is based on the observed retention of stereospecificity. This would not be expected for a stepwise mechanism. The rate of reaction has been found to be independent of solvent polarity. However if the betaine mechanism was in operation the rate would be expected to be enhanced in a polar solvent due to charge buildup in the transition state.

Stereoselectivity in the Diels-Alder reaction may also be explained in terms of frontier orbitals. Diels-Alder reactions in general give endo adducts predominantly, exemplified in **scheme 1.1** by the Diels-Alder reaction between maleic anhydride and cyclopentadiene.

Scheme 1.1



Formation of the thermodynamically less stable endo adduct is accounted for by overlap of secondary frontier orbitals not directly involved in formation of the new bonds.

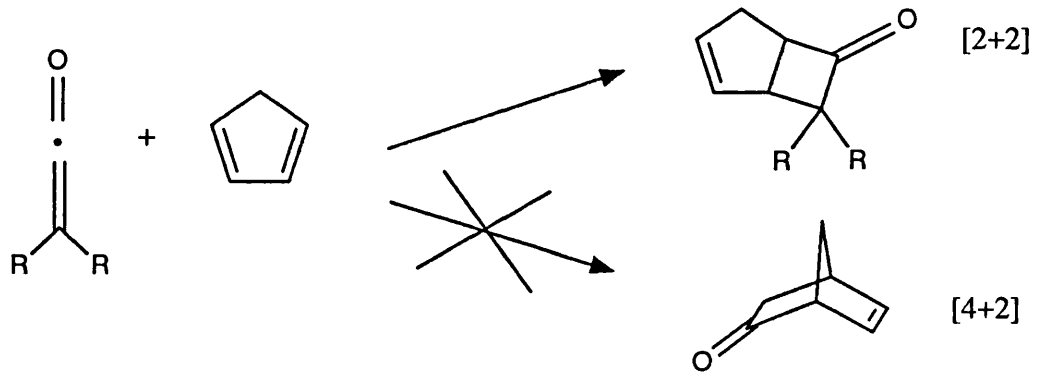
The secondary orbital interactions that are possible in the endo transition state will lower the energy of the transition state relative to the exo transition state and will result in formation of the endo adduct over the exo adduct. Similar secondary orbital interactions are not possible in the exo transition state. This effect is known as the "endo rule" and is often observed for in 4+2 cycloadditions. It should be noted that the "endo Alder rule" does not apply to reactions under thermodynamic control.

A second rule associated with the stereochemical outcome of a Diels-Alder reaction is the "*cis*-rule". This states that the relative stereochemistry of the substituent groups in the diene and dienophile are maintained in the product of cycloaddition.

1.2 Ketene Equivalents : Cyclobutanone formation

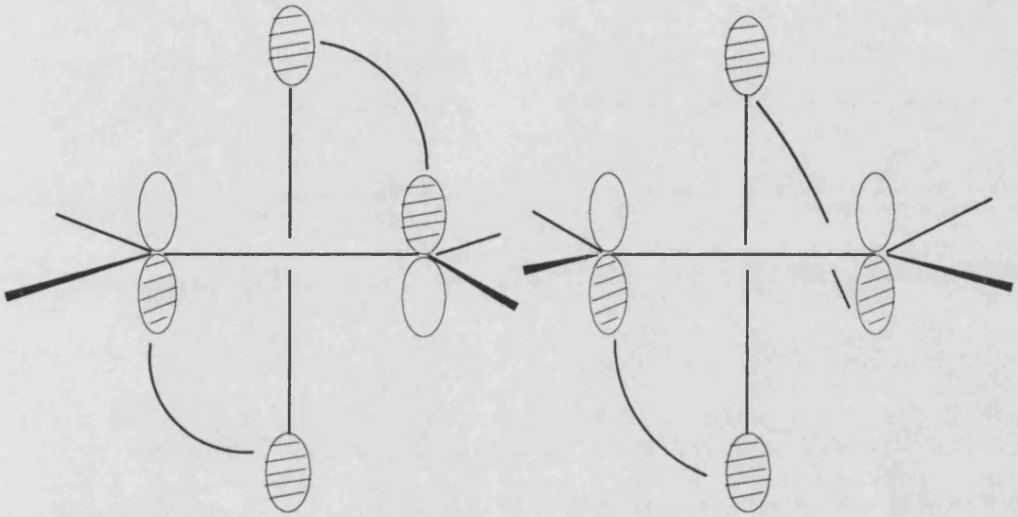
This thesis is concerned with the formation cyclic ketones which are important intermediates in organic synthesis. Direct reaction between ketene and cyclopentadiene does not give the [4+2] Diels-Alder reaction but the product from a [2+2] cycloaddition (**scheme 1.2**).[12]

Scheme 1.2



For the [2+2] type of cycloaddition to occur the π systems of the two components must be orthogonal **figure 1.2.** This pathway is normally forbidden due to steric hindrance and transition state strain required to maintain effective orbital overlap.

Fig 1.2



Ketenes unlike simple olefins show a more favourable steric situation. The presence of an orthoganal p orbital contributes two extra bonding interactions which are not present in the [$\pi 2_s + \pi 2_a$] reaction for simple olefins. In ketenes the vacant p orbital is the unoccupied π^* C=O orbital and it is this low lying LUMO which accounts for ketenes exceptional electrophilic reactivity. [$\pi 4s + \pi 2s$] Cycloadditions are further disfavored due to unfavourable interactions of the oxygen lone pair with the diene.

To allow the Diels-Alder reaction to occur, features that enhance the [2+2] mode of cycloaddition need to be removed. To achieve this the carbonyl group is masked and the [4+2] reaction becomes the faster of the two possible proccesses. By choosing a masking group that may subsequently be transformed back to a ketone after the cycloaddition the overall effect will have been the [4+2] cycloaddition. Compounds with such masked carbonyl groups are known as a ketene equivalents.

Ketene equivalents have been employed in synthesis to produce synthetic

intermediates in both racemic[13] and enantiomerically pure[7] forms. The following chapters exemplify the ketene equivalents used in the literature to date and describe the rationale behind their design.

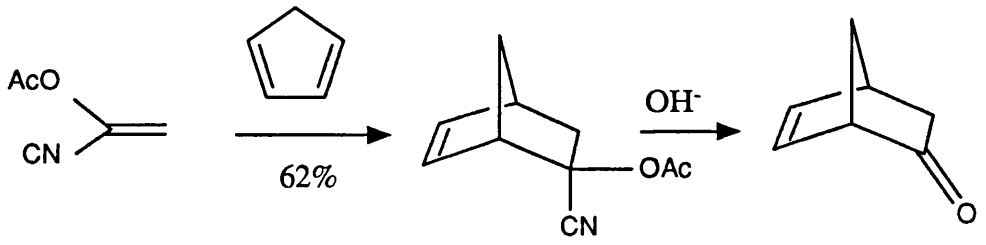
1.3 Ketene equivalents

1.3.1 α-Acetoxyacrylonitrile

α-Acetoxyacrylonitrile was the first ketene equivalent and was introduced by Bartlett et al[14] in 1956. Prior to this (**1**) was synthesised by oxidation of norbornenol.[15] α-Acetoxyacrylonitrile was synthesised by reaction between ketene and hydrogencyanide followed by acetylation.[16]

The Diels-Alder reaction of the cyanoacetate (**3**) and cyclopentadiene (**scheme 1.3**) proceeded in 62% yield when the dienophile was heated to 100°C for three hours in cyclopentadiene.

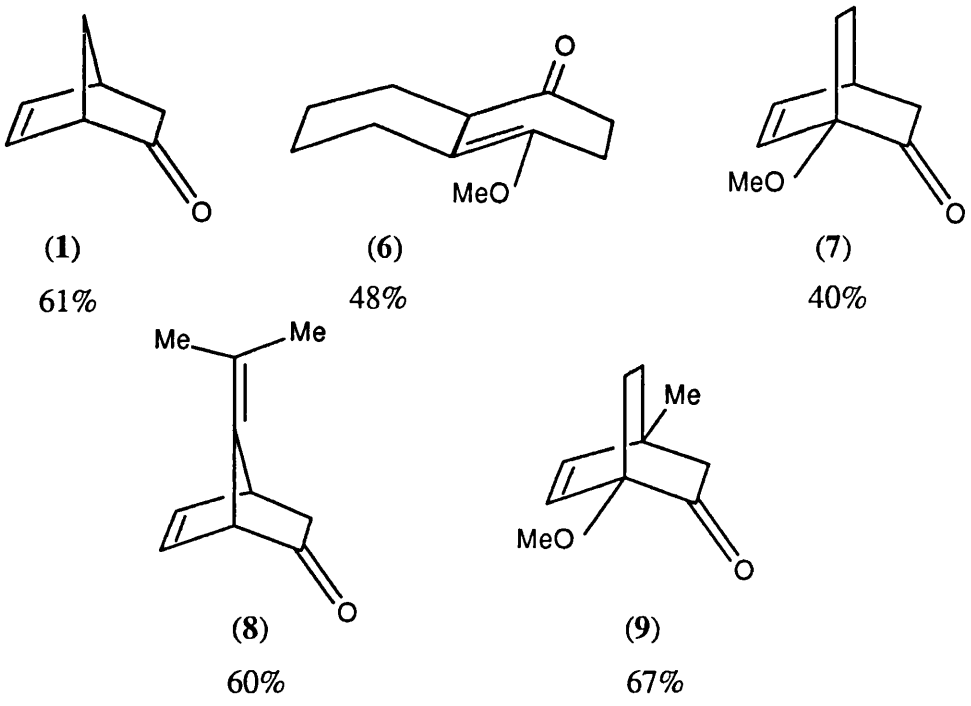
Scheme 1.3



(3) (4) (1)

Treatment of the Diels-Alder adduct with sodium hydroxide afforded the required ketone (**1**) in 51% overall yield. α-Acetoxyacrylonitrile was readily available and has subsequently been used in synthetic pathways towards the synthesis of a range of bicyclic ketones 1[17], 6, 7[18], 8, 9[19], **figure 1.3.**

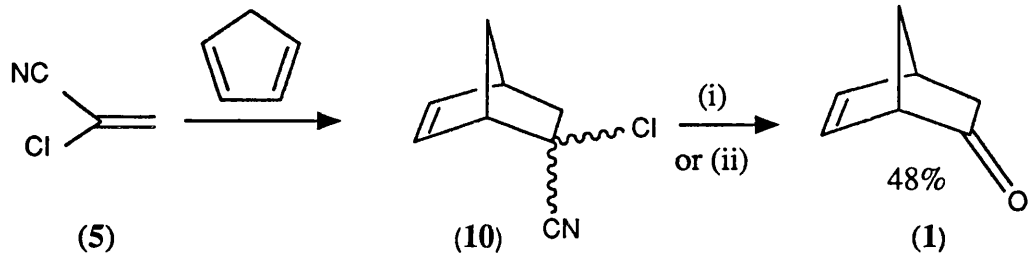
Fig 1.3



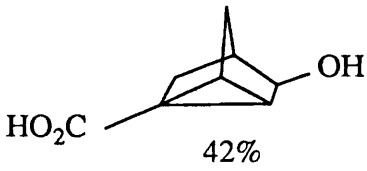
1.3.2 α-Chloracrylonitrile

α-Chloroacrylonitrile (**5**) was prepared by Passiuirta[21] and Kriger et al[22]. α-Chloracrylonitrile unlike acetoxyacryonitrile [20] is readily available and formed [4+2] adducts more readily than (**3**). The cycloadducts were transformed into the ketones (**1**) under mild conditions. However less reactive dienes required reaction temperatures of 140-160°C (**scheme 1.4**), often producing polymeric tars.

Scheme 1.4



(5) (10) (1)



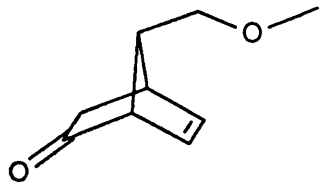
42%

(11)

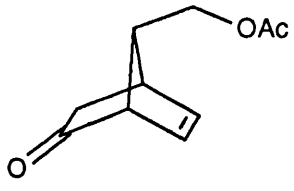
Reagents: (i) KOH, H_2O (ii) S^{2-}, KOH_{aq}

Production of polymeric tars limited the use of (5) in synthesis of some ketones, however as shown in **figure 1.4** the dienophile was applied to the synthesis of a range of bicyclic ketones.

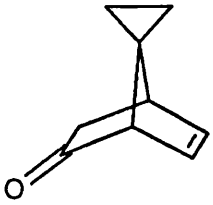
Fig 1.4



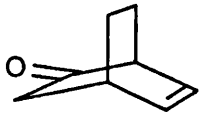
(12)
80%



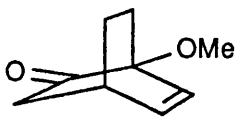
(13)
40%



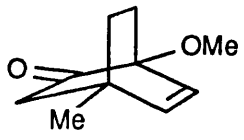
(14)
60%



(15)
100%



(7)
80%



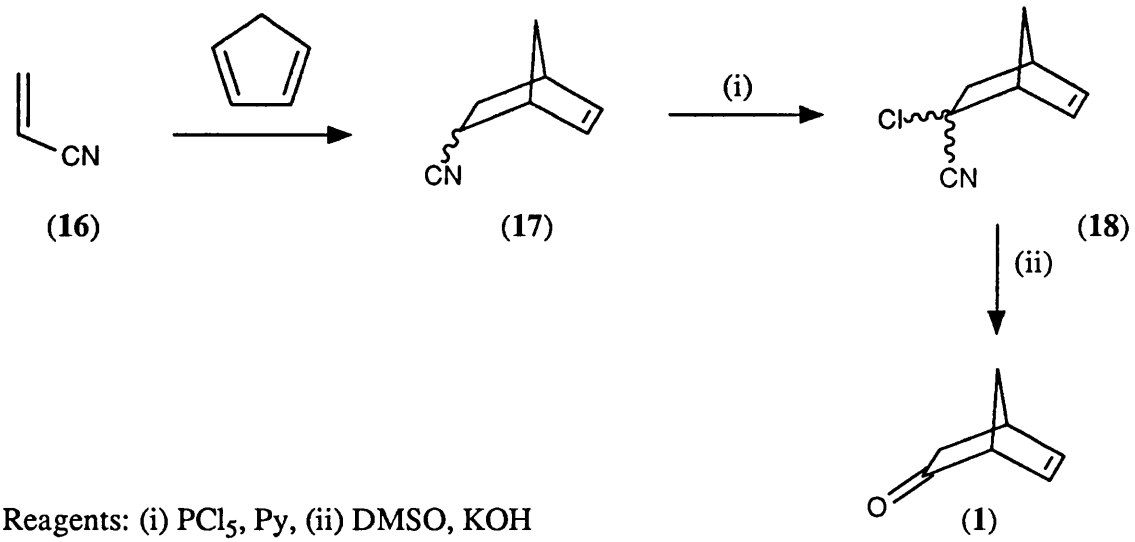
(8)
92%

The attractive feature of this dienophile lay in its mild hydrolytic conditions.

1.3.3 Acrylonitrile

A modification of the chloroacrylonitrile dienophile acrylonitrile (**16**) has been used as a ketene equivalent affording bicyclic ketones as shown in **Scheme 1.5**

Scheme 1.5



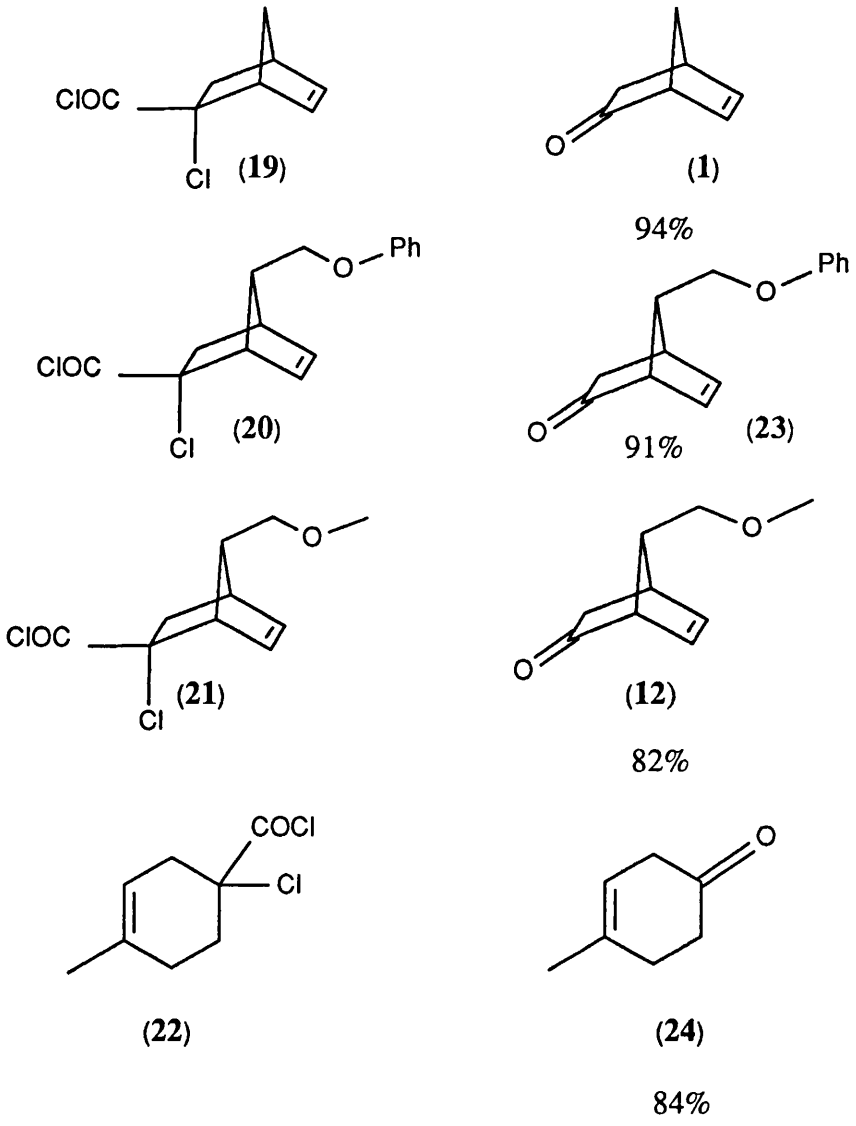
Reagents: (i) PCl_5, Py, (ii) DMSO, KOH

The mild hydrolysis of acrylonitrile cycloadducts was achived by initial chlorination[29] with PCl_5 followed by hydrolysis in the same manner as for the adducts described in section 1.2. The reactivity was found to be similar to α-chloroacrylonitrile, requiring elevated temperatures , over 60°C or catalysis with copper fluoroborate to effect cycloaddition.[30] Under such conditions 5-substituted cyclopentadienes, required for the prostaglandin intermediates 7-syn substituted [2.2.1]hept-2-enones, were found to undergo prototropic isomerization. For Corey's prostaglandin work, chloroacryloyl chloride was developed as a more reactive dienophile.

1.3.4 Chloroacryloyl Chloride

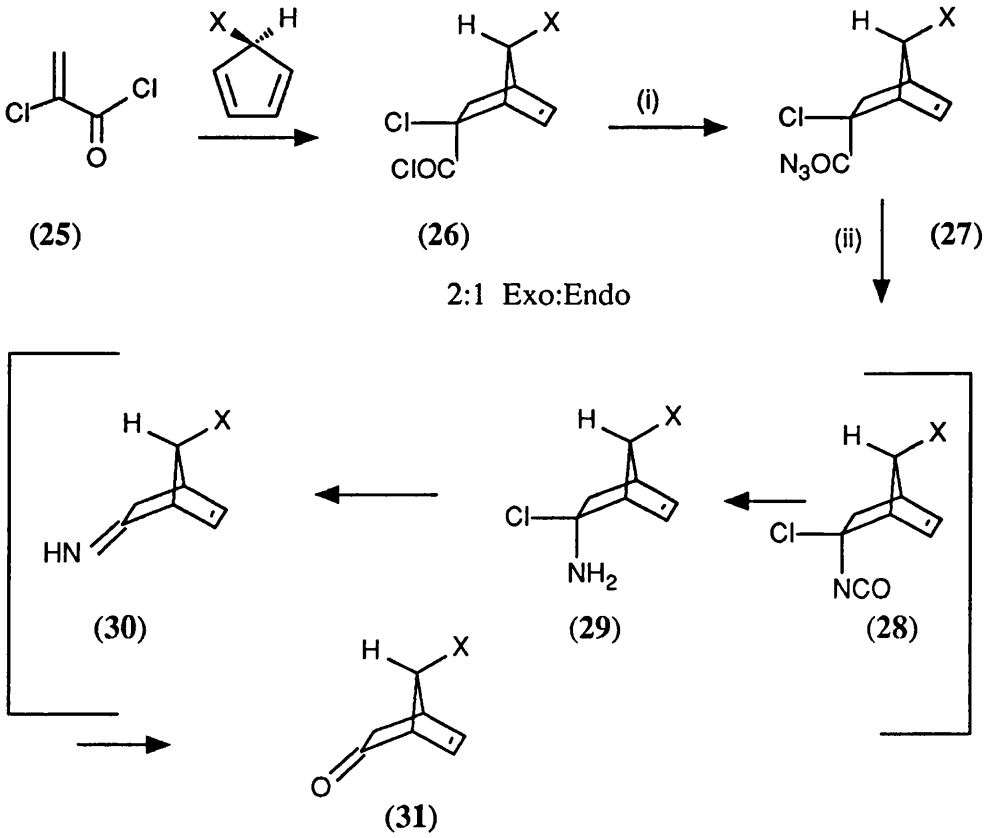
Corey et al[31] found that chloroacryloyl chloride (**25**) was a highly reactive dieneophile which reacted with cyclic dienes at low temperature. This allowed reaction with 5-substituted 1,4-cyclopentadienes, without isomerization of the diene to a more reactive diene. (**figure 1.8**).

Fig 1.8



Diels-Alder adducts eg. (22) from acyclic dienes such as isoprene are also obtainable by this method. The use of strong base in the hydrolysis of previous dienophiles precluded reaction with acyclic dienes due to subsequent isomerisation of the double bond into conjugation with the carbonyl group.. As shown in **scheme 1.6,** the initial Diels-Alder adducts may be transformed into bicyclic ketones by a sequence involving a Curtius rearrangement.

Scheme 1.6



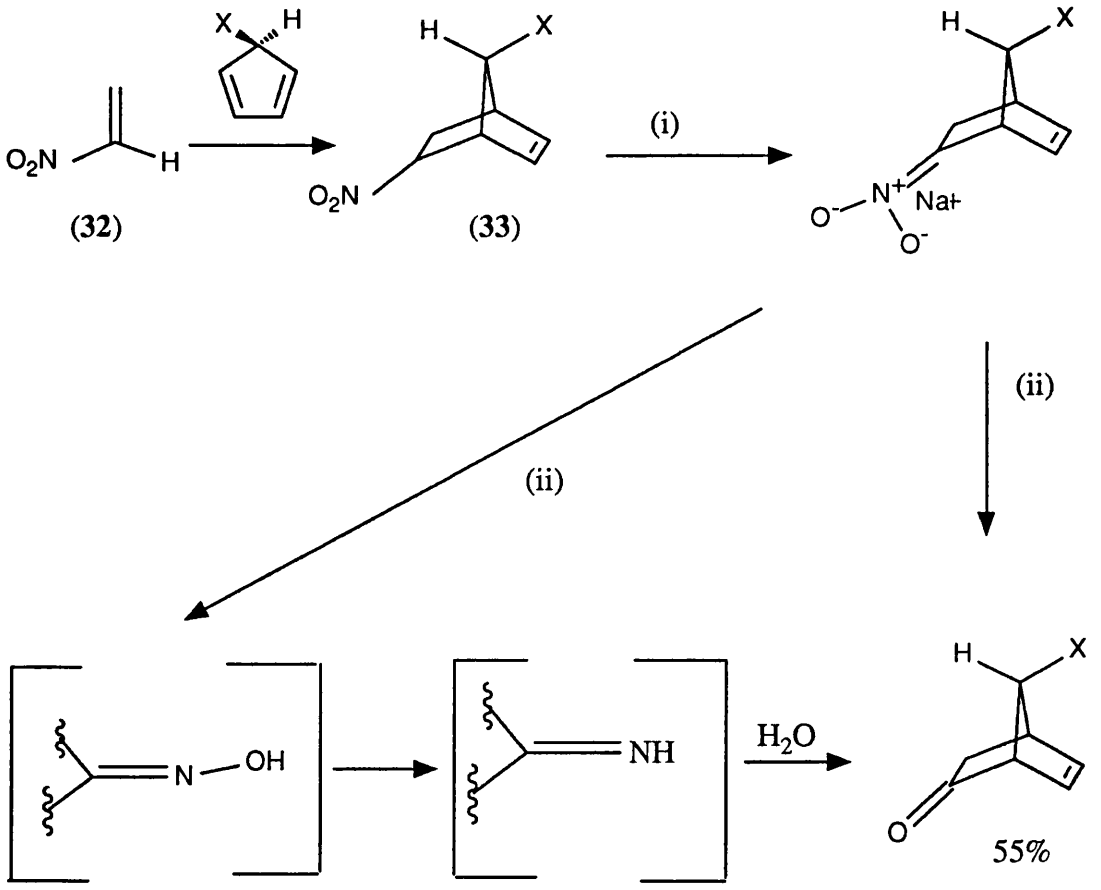
Reagnts: (i)NaN_3, $MeOCH_2CH_2OMe$, 2Hr, (ii) CH_3CO_2H/H_2O 55°C, 4Hr.

The use of this dienophile was hampered by difficult preparation[32] and the hazardous azide intermediate formation in the conversion to the required ketone(**1**). The identification of nitroethene as a ketene equivalent solved the afore mentioned problems.

1.3.5 Nitroethane

Nitroethene (**32**) has been found to react with sensitive cyclopentadienes even at -100°C and is readily transformed to bicyclic ketones by treatment of the nitronate salts with titanium (III) chloride[33] (**Scheme 1.7**).

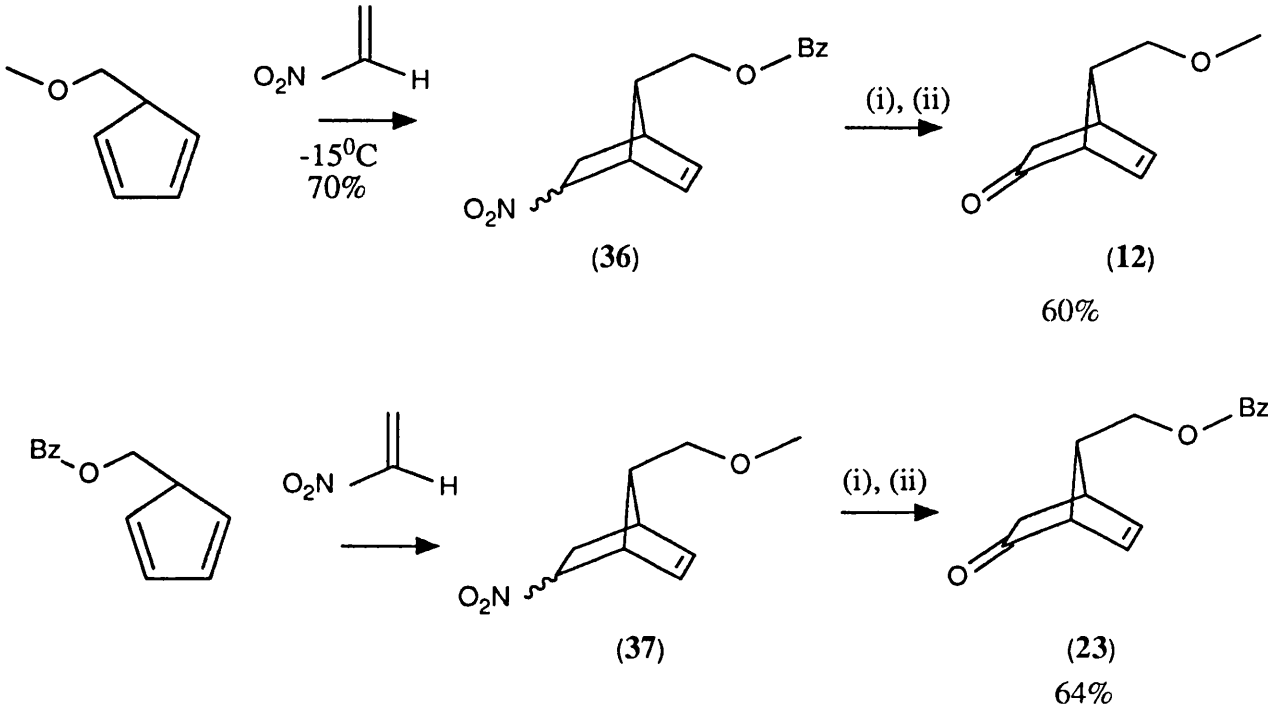
Scheme 1.7



Reagents: (i) $NaOCH_3$, MeOH, (ii) $TiCl_3$, pH 5-6

Nitroethene has found wide spread application organic synthesis,[34,35] allowing access to prostaglandin intermediates. (**Scheme 1.8**).

Scheme 1.8



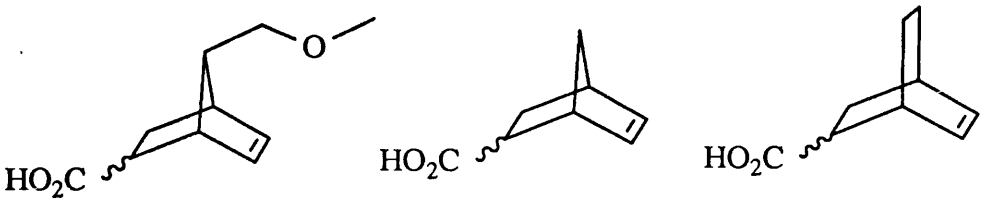
Reagents : (i) CH_3OH/ $NaOCH_3$,, (ii) $TiCl_3$/ NH_4OAc.

1.4.0 Other ketene equivalents used in synthesis

1.4.1 Acrylic Acid

Acrylic acid has also been found to be a good ketene equivalent[36] showing high reactivity and mild hydrolytic conditions. The carboxylic acid group can be readily converted to a carbonyl group making this dienophile compatible with base sensitive 5-substituted cyclopentadienes (**figure. 1.6**)

Fig 1.6



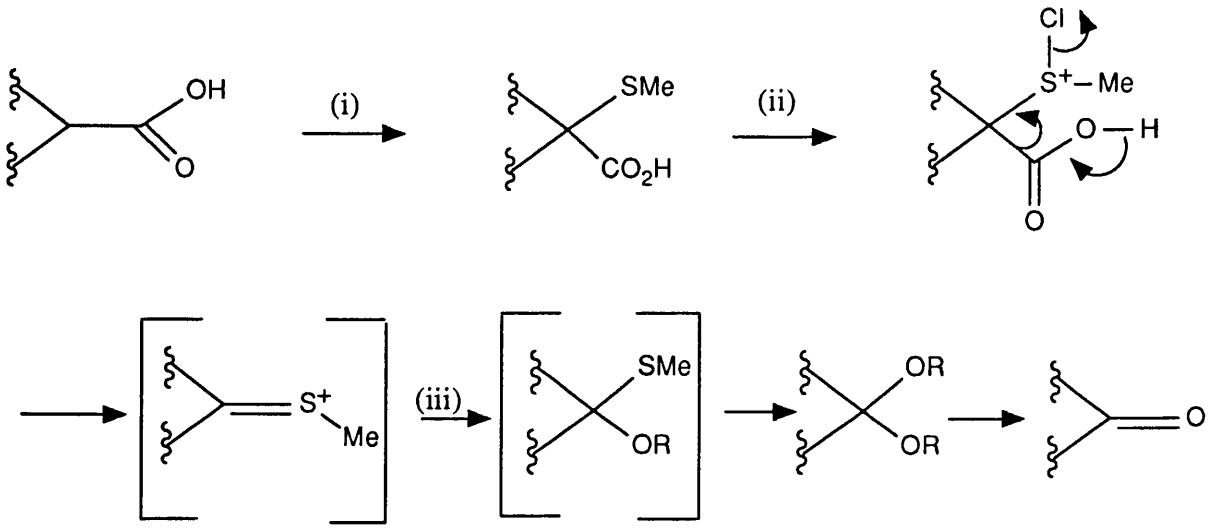
(38) 62%

(39) 60%

(40) 44%

Hydrolysis was affected by a two step procedure involving oxidative decarboxylation[36]. Formation of the carboxylate dianion with lithium diispropylamide was followed by addition of dimethyldisulfide. Chlorination of the sulfide with N'chlorosuccinamide gave a ketal which was readily hydrolysed to the ketone in aqueous acetic acid, as illustrated in **scheme 1.9**.

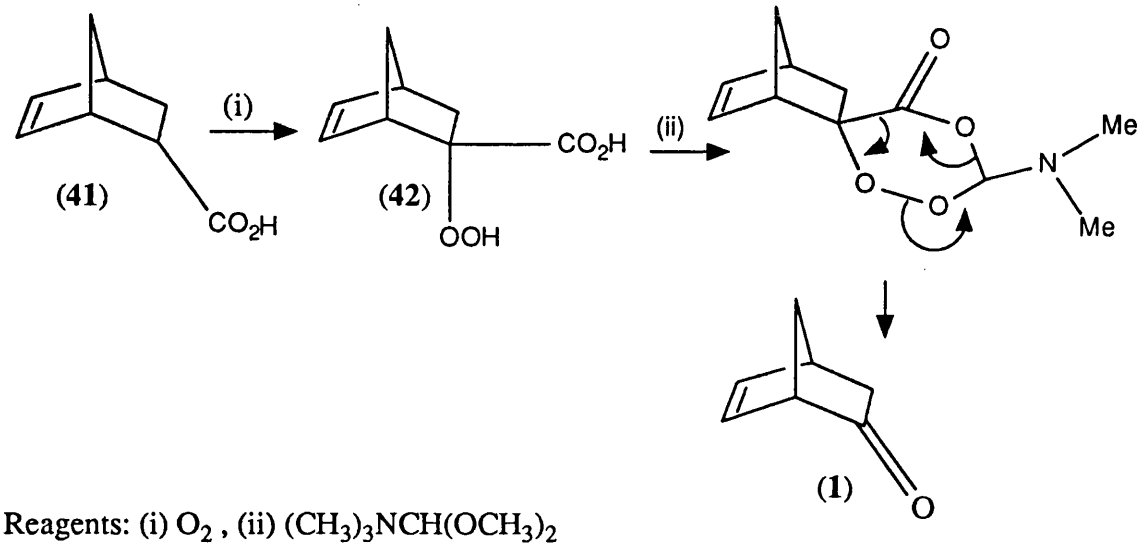
Scheme 1.9



Reagents (i) LDA, MeSSMe, (ii) NCS, (ii) HOR'

The alternative method employed by Lipshutz et al[37] involved oxygenation of the dianion affording an α hydroperoxide which undergoes carboxylative elimination to give ketones in good yield (**Scheme 1.10**).

Scheme 1.10

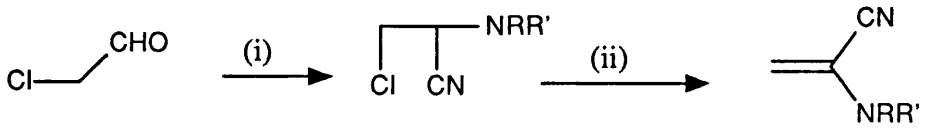


Reagents: (i) O_2 , (ii) $(CH_3)_3NCH(OCH_3)_2$

1.4.2 Cyanoenamines

Cyanoenamines[39] have been used as ketene equivalents affording adducts with good endo selectivity. The enamines were synthesised as shown in **scheme 1.11**.

Scheme 1.11



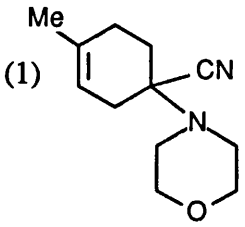
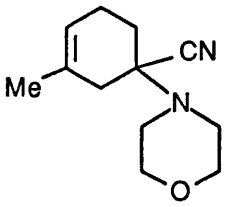
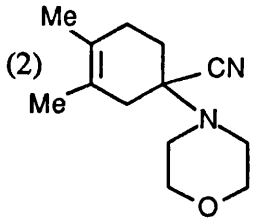
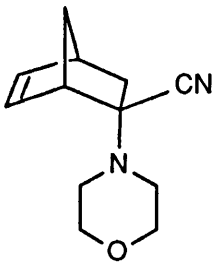
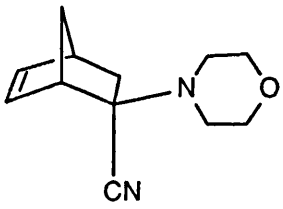
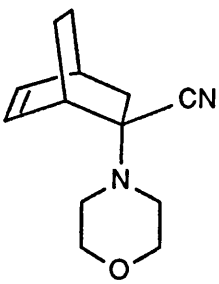
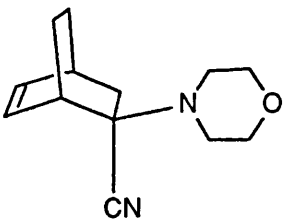
(**45**) R,R'= $(CH_2)_2O(CH_2)_2$

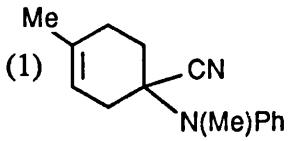
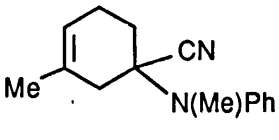
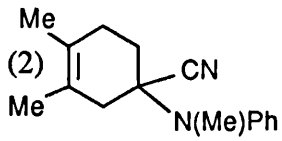
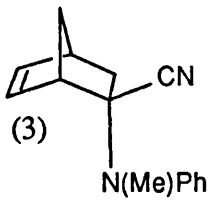
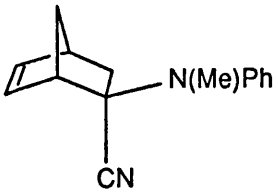
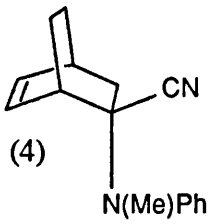
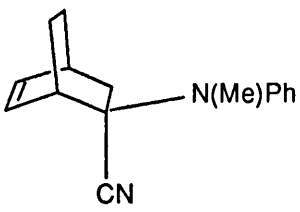
(**46**) R=Me, R=Ph

Reagents: (i) RR'NH, HCl, NaCN, (ii) Base

The chloroacetaldehyde was treated with the appropriate amine hydrochloride followed by sodium cyanide to give the β-chloroaminonitrile. Subsequent base elimination of the chloride gave the required alkenes (**45,46**)[40]. The Diels-Alder reactivity of the cyanoenamines was investigated with four dienes, **figure 1.7.**

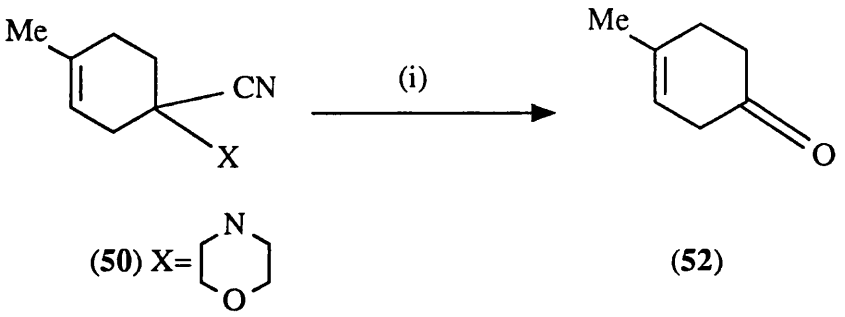
Fig 1.7

			Time (hr)	Yield	
(1)			6	66	
(2)			6	81	
	EXO	ENDO			ENDO:EXO
(3)			20	19	NOT DETERMINED
(4)			6	20	79:21

		Time (hr)	Yield	a:b
(1)  (a)  (b)		6	24	100:0
(2) 		6	18	
EXO	ENDO			Endo:Exo
(3) 		6	55	55:54
(4) 		6	65	53:47

Stella et al investigated the influence of Lewis acids and solvent on dienophiles (**45**) and (**46**), both of which were found to have no effect on rate or selectivity. Transformation of the cyanoamine adducts (**50,51**) into the bicyclic ketone (**52**) was achieved with silver nitrate in ether and water in 81% yield (**Scheme 1.12**).

Scheme 1.12



(**50**) X=

(**52**)

(**51**) X= N(Me)Ph

Reagents: (i) $AgNO_3$, Et_2O-H_2O, 20°C, 1hr

Hydrolysis was also effected with copper sulfate pentahydrate in refluxing methanol/water for 2hr affording the bicyclic ketone (**52**) in a 30-80% yield.

There is currently great interest in asymmetric synthesis. In this respect the Diels-Alder reaction has received considerable attention with the development of chiral dienes[41], catalysts[42] and dienophiles[43]. Previous chiral ketene equivalents have been based on chiral acrylates, chiral vinyl sulfoxides and chiral oxazolinones.

1.5.0 Chiral Acrylate Dienophiles

1.5.1 Introduction

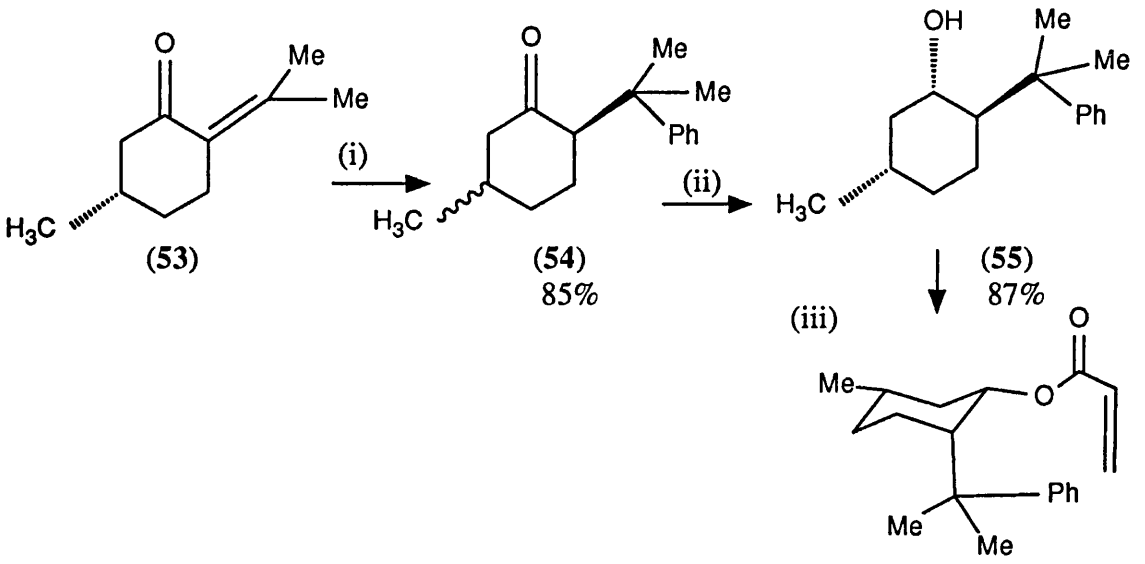
Chiral acrylates have been employed in asymmetric Diels-Alder reactions since 1966[44]. Walborsky et al[45] showed that partial asymmetric induction in the Diels-Alder reaction between (-) dimethylfumerate and 1,3-butadiene was possible, although induction of only 3% ee was observed.

Chiral acrylates as ketene equivalents have been employed in a range of synthesis, utilizing the readily available source of chirality from naturally occurring and synthetic chiral alcohols.

1.5.2 Synthesis of Chiral Acrylates

The synthesis of 8-phenylmenthyl acrylate is shown in scheme 1.13[46]. Chiral alcohols were prepared from the corresponding ketones by reduction with sodium or lithium[47]. **Scheme 1.13** shows a typical example in which (-) 8-phenyl-menthol (**55**) was synthesised from pure S(-) pulegone (**53**) by treatment with phenyl magnesium bromide in the presence of cuprous chloride. Treatment of alcohol (**55**) with triethylamine and acroyl chloride gave the chiral acetate (**56**) in 97% yield.

Scheme 1.13

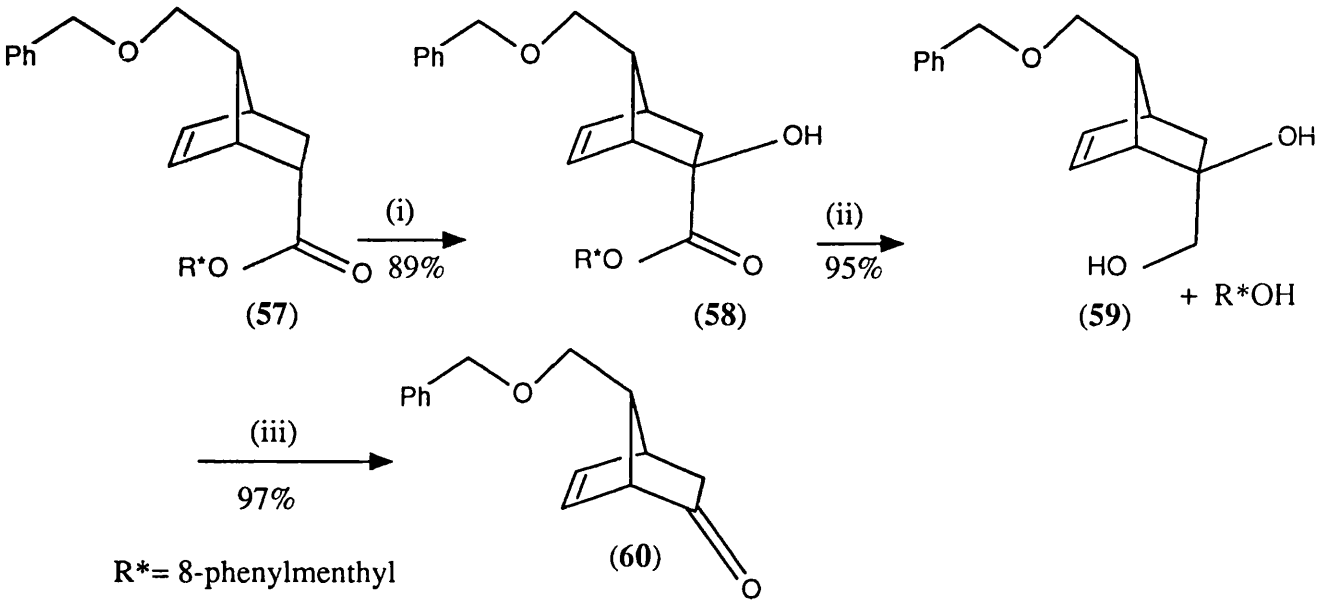


Reagents: (i) PhMgBr, $CuCl_2$ (ii) a, KOH, EtOH b, Na, iPrOH, Tol
(iii) $CH_2CHCOCl$, Et_3N, DMAP, 0°C, CH_2Cl_2.

1.5.3 Hydrolysis of Acrylate Auxillary

One of the requirements of a ketene equivalent was that the carbonyl equivalent may be easily unmasked, subsequent to the Diels-Alder cycloaddition affording the required ketone. In the case of acrylate Diels-Alder adducts the ketone may be generated *via* a three step process shown in scheme 1.14[48].

Scheme 1.14



Reagents: (i) LDA, oxygenated THF, triethylphosphite. (ii) LAH, THF, (iii) ^{t}BuOH, $NaIO_4$

Hydroxylation of the adduct (**57**) followed by reduction to the diol (**59**) and subsequent periodate cleavage gave the ketone (**60**).

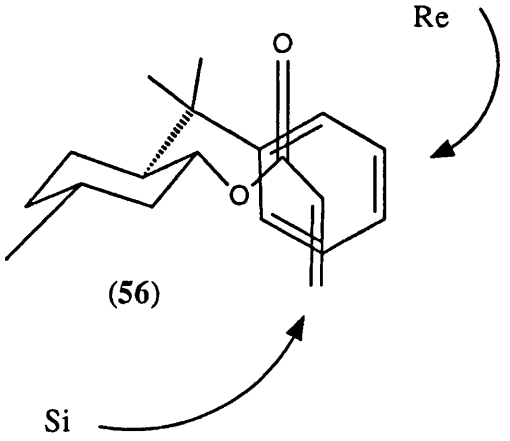
From this it can be seen that chiral acrylates may be employed as chiral ketene equivalents. The auxiliary may be removed easily in the presence of a range of functional groups using this procedure.

1.5.4 Menthyl Acrylates

The use of acrylate derived dienophiles in asymmetric Diels-Alder reactions was reported independently by Sauer et al and Farmer and Hamer.[44] Reaction of (1*R*, 2*S*, 5*R*) -(-)menthyl acrylate with cyclopentadiene gave low enantiomeric excess for the uncatalysed reaction and moderate (82% ee) for the Lewis acid catalysed reaction.

Corey developed 8-phenylmenthyl acrylate (**61**)[48] for the synthesis of prostaglandin intermediates. This type of dienophile exhibited greater differentiation of the diastereotopic faces of the acrylate dienophile, **figure 1.11.**

Fig 1.11

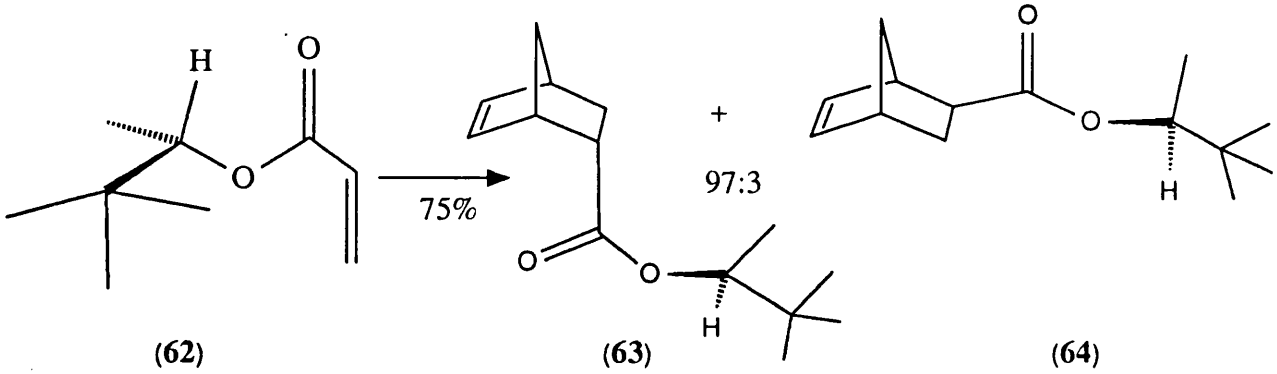


It was proposed that the acrylate adopted an s-*trans* conformation resulting in blockage of the *re* face by the phenyl substituent. This conformation was thought to be favoured due to π stacking between the acrylate and aromatic ring.
The result of these interactions afforded Diels-Alder cycloadducts with cyclopentadiene, catalysed by stannous (IV) chloride, in (+) 89% ee[50] (corrected from the original figure quoted by Corey[48] of 99% ee).

1.5.5 (S)-(+)-1,2,2-Trimethylpropyl Acrylate

Subsequent to Corey's work Greene and LeDrian employed the use of (S)(+)-1,2,2 trimethylpropyl acrylate in an asymmetric Diels-Alder reaction in a synthesis of Brefeldin-A.[51] In the Diels-Alder reaction adducts were formed (97:3 endo:exo) which were found to have (1-R) and (1-S) configurations, respectively, (**Scheme 1.16**). Conversion to norbornenone (**1**) was effected as previously described in Section 1.5.3.

Scheme 1.16

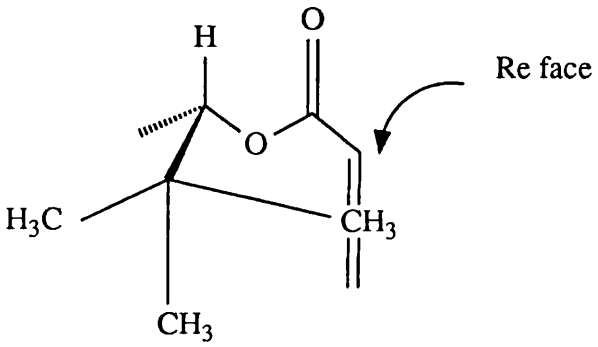


(**62**) (**63**) (**64**)

Reagents: (i) Cyclopentadiene,BF_3•OEt_2, CH_2Cl_2, -78°C

The diastereoselectivity in this reaction has been attributed to preferential approach of the diene from the face opposite to the bulky ^{t}butyl group, **figure 1.12.**

Fig 1.12



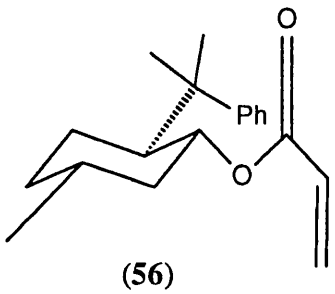
(62)

The synthetic utility of this type of acrylate dienophile is restricted due to problematic separation of the enantiomers of oily chiral alcohols.

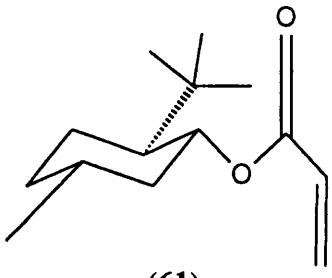
Oppolzer[52] reinvestigated the degree of diastereoselectivity in the reaction of cyclopentadiene with a range of chiral acrylates by preparing the Moshers acid derivative[53] of the endo alcohols. Reduction of the ketone followed by ^{19}F NMR analysis with the chiral shift reagent $Eu(fod)_3$ determined the enantiomeric excess of the auxiliary alcohol. **Table 1.2** shows the optimum conditions for reaction between 8-phenylmenthyl acrylate.

TABLE 1.2

Acrylate	Equivalent Lewis Acid	Solvent	Temperature 0°C	Time (h)	Yield %	ENDO EXO	%ee 2-R-()
(61)	1.0 $SnCl_4$	TOL	0	0.5	-	-	51
(56)	1.5 $SnCl_4$	TOL	0	3.5	95	84:16	89
(61)	0.7 $ALCl_3$	CH_2Cl_2	-55	-	-	-	48
(56)	0.7 $ALCl_3$	CH_2Cl_2	-20	3.5	90	91:9	65
(56)	0.7 $ALCl_3$	TOL	-20	3.5	16	92:8	52
(56)	1.5 Me_2ALCl_3	CH_2Cl_2	0	3.5	95	89:11	64
(61)	1.5 Me_2ALCl_3	CH_2Cl_2	0	3.5	7.3	92:8	47
(56)	1.5 Me_2ALCl_3	TOL	0	3.5	81	88:12	55
(56)	1.5 $TiCl_4$	CH_2Cl_2	-20	3.5	65	92:8	62
(61)	1.5 $TiCl_4$	CH_2Cl_2	-20	3.5	83	89:11	90



(56)

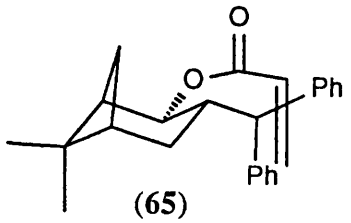


(61)

Under all the conditions given in **table 1.2** the 2(R) enantiomer was produced in excess and 8-phenylmenthyl acrylate was found to show the highest diastereoselectivity. The origin of the diastereoselectivity was studied by Oppolzer[53] by investigating a verity of

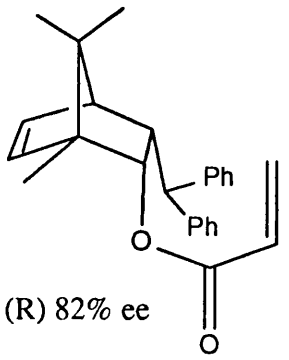
chiral alcohol auxiliaries **Figure 1.3**.

Fig 1.13



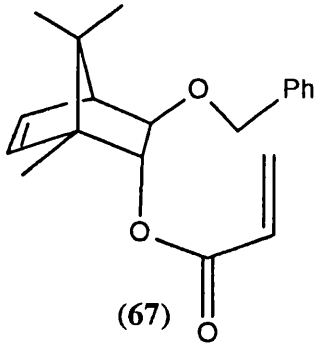
(65)

Endo (R) 89% ee



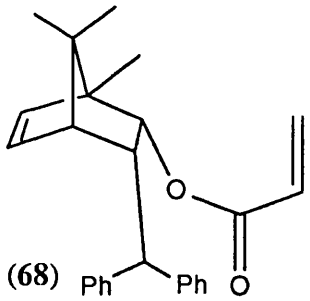
(66)

Endo (R) 82% ee



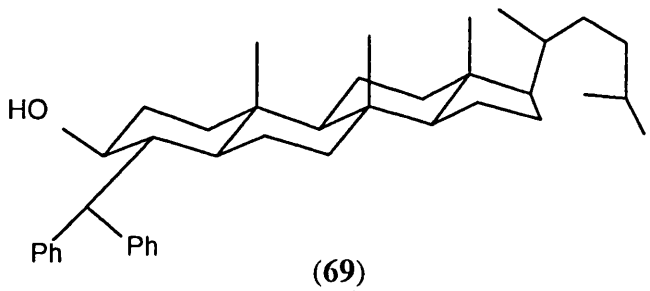
(67)

Endo (S) 88% ee



(68)

Endo (S) 82% ee

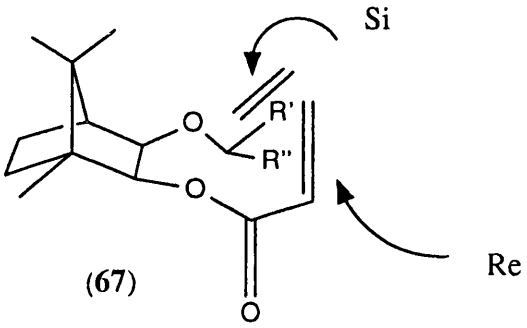


(69)

Endo (S) 85% ee

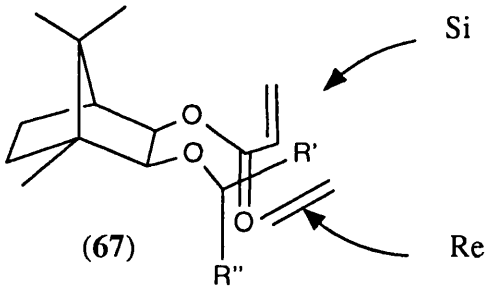
Entries (**65**) and (**66**),(**figure 1.14**) are *Re* face directing acrylates. They were found to give high asymmetric induction as well as being available in both antipodes.

Fig 1.14



(67)

			Adduct config^{n}	ee%
(a)	R'= Ph	R''= Ph	S	64
(b)	R'= Nap	R''= H	S	69
(c)	R'= Ant	R''= H	S	54
(d)	R'= ^{t}Bu	R''= H	S	97



(67)

(e)	R'=Ph	R''=Ph	R	91
(f)	R'= Nap	R''=H	R	92
(g)	R'=^{t}Bu	R''=H	R	99

1.5.6 π-Stacking in acrylate dienophiles.

In this study a range of isobornylcamphor aryl ethers with varying size of aromatic surface area were investigated to probe the presence of π stacking. In the Lewis acid catalysed reactions it was found that titanium tetrachloride resulted in rapid ether cleavage and so the milder Lewis acid, titanium dichlorodiisopropoxide, was

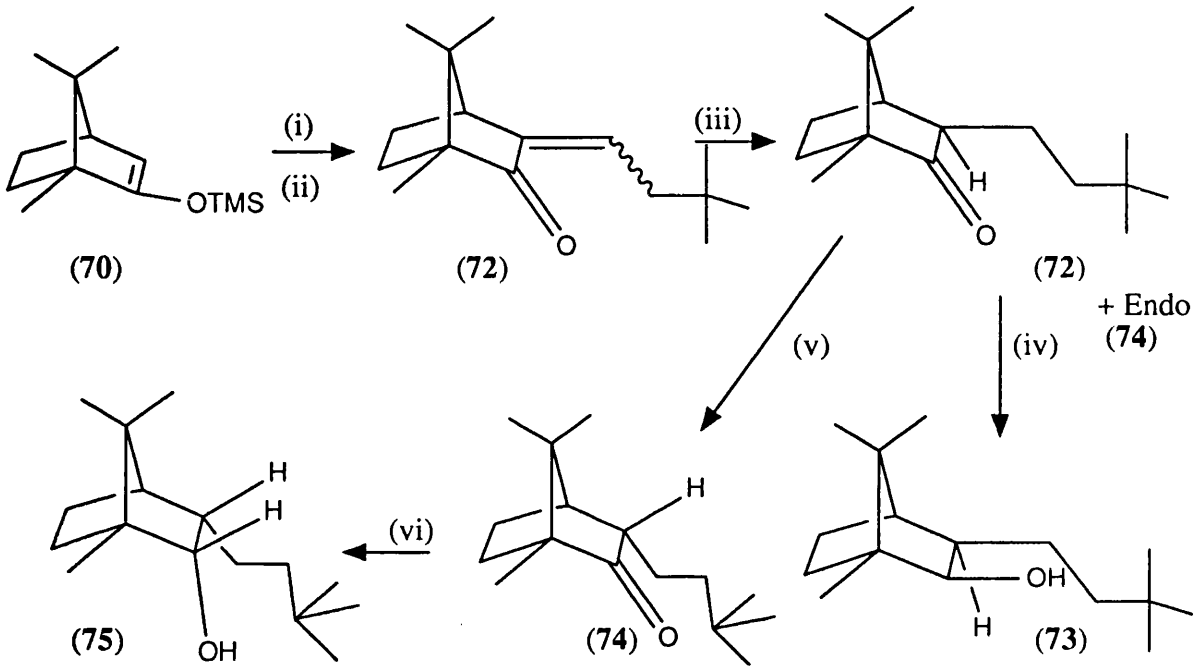
employed. Although the chemical yield was increased the diastereoselectivity was much reduced from 88% to 46%. Increasing the size of the aromatic group increased selectivity. However, to investigate the nature of the asymmetric induction an alkyl ether, (**67f**)was prepared to distinguish between π,π aryl/acrylate orbital overlap and steric crowding. The cycloadditon of this acrylate (**67d**) (**67f**) showed higher selectivity than that of the hyroxyisobornyl-methyl aryl ethers (a) and (e). Examination of the neopentyl ethers shows that a staggered conformation of the neopentyl side chain would effect strong facial differentiation under steric control.

The extra induction of (g),99% ee compared to (d) 97% ee has been attributed to repulsion of C_{10} methyl and the ether chain, pushing the ether chain nearer to the acrylate increasing the effective shielding.

Although π stacking interactions may be involved and have been evoked in other examples[55], steric hindrance is attributed as the main factor governing asymmetric induction.[56]

A second series of camphor based acrylates was investigated by Oppolzer,[57] where the ^{t}butyl group was attached to the bornenol skeleton by a carbon chain link instead of an ether linkage. The chiral alcohols were synthesised as shown in **Scheme 1.18.**

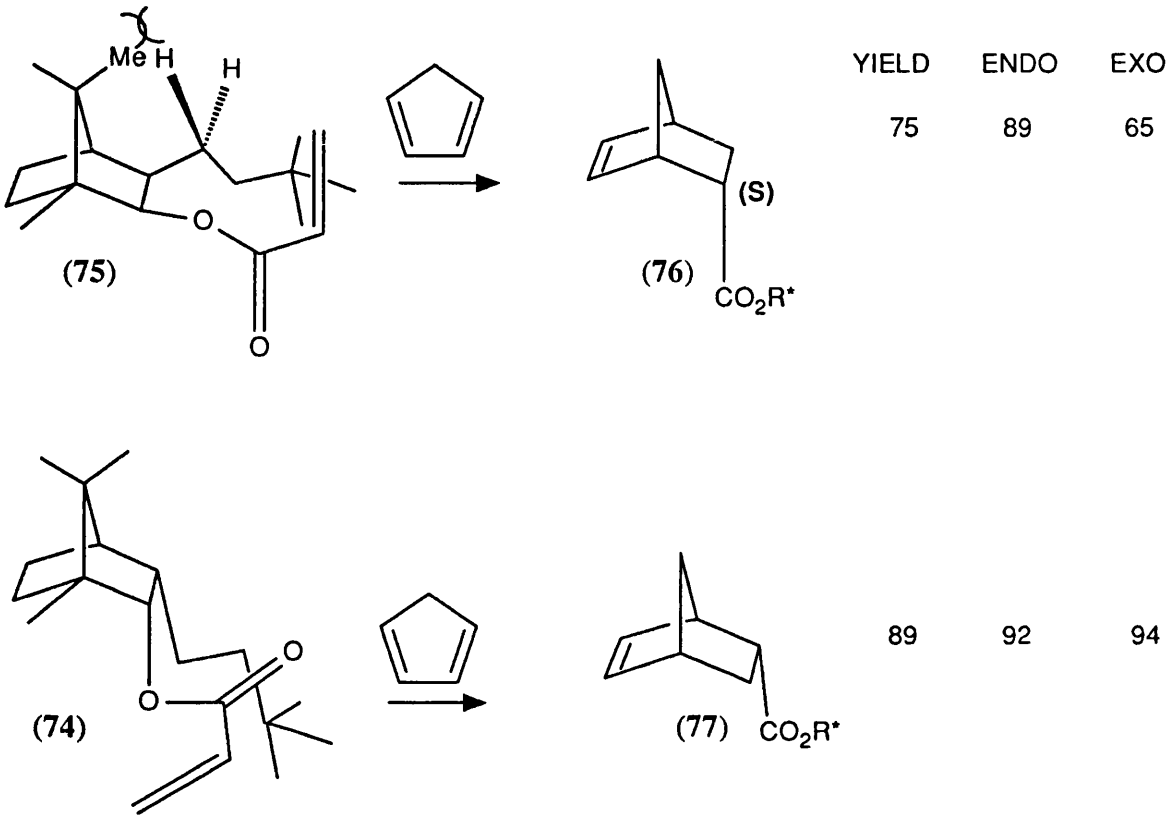
Scheme 1.18



Reagents: (i) $(CH_3)_3CCHO$, $TiCl_4$, (ii) a NaH, THF/HMPA, imidazole, b CS_2, 3Hr, $(CH_3O)SO_3$ (iii) H_2, Raney Nickel. (iv) L Selectride (v) ^{t}BuOK, ^{t}BuOH, (vi) Na(Hg), iPrOH, Na_2HPO_4

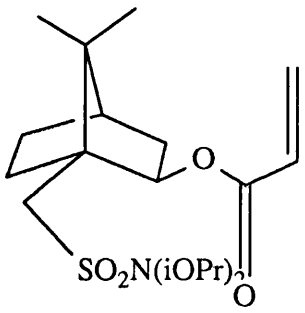
Aldol reaction of the silyl enol ether (**70**) followed by elimination gave a mixture 6:1 of enone (**71**). Hydrogenation of (**71**) afforded an 83:17 ratio in favour of the exo ketone (**72**). The exo ketone was equilibrated to the more stable endo ketone (**74**) with potassium ^{t}butoxide and reduced with sodium/mercury amalgam to afford the *cis* endo alcohol which was transformed to the required acrylate as previously described. Both the *cis* endo (**75**) and the *cis*-exo (**73**) derived acrylates were reacted with cyclopentadiene using $TiCl_2(iPrO)_2$ as a catalyst, **Scheme 1.19**.

Scheme 1.19

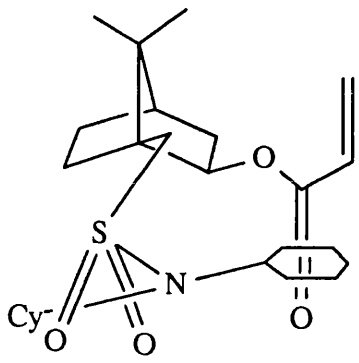


These crystalline derivatives appear to be more attractive as they are available in higher yields. The replacement of the ether oxygen confers greater stability to the auxiliary and should allow catalysis by $TiCl_4$. Other camphor based acrylates were designed to improve crystallinity which would aid purification. **Figure 1.15** shows the acrylates and the enantiomeric excesses observed[57].

Fig 1.15



(78)[55]



(79)

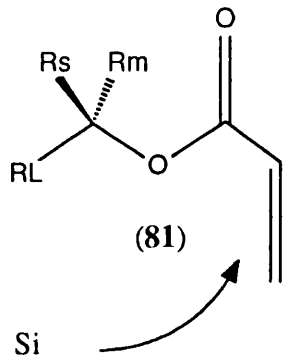
Cyclopentadiene was found to attack as expected from the opposite side to the bulky C-10 sulfonamide group. In the titanium dichlorodiisopropoxide catalysed reaction the endo:exo ratio was found to be 97:3, 88% de, in the R configuration. The minor exo adduct was removed by recrystallisation. In the cyclohexyl series (**79**) the crystalline cycloadducts were obtained in 97% yield with a 96:4 endo:exo ratio, 93% de. The stereoselectivity of this dienophile has been shown,using x-ray studies[58], to originate from two controlling factors. Firstly, the acrylate adopts an s-*trans* conformation and secondly one of the lone pairs on nitrogen one is found to bisect the O-S-O angle causing a cyclohexyl ring to block the *re* face of the acrylate. Replacement of the cyclohexyl groups in (**80**) with aryl groups[59] reduced the diastereoselectivity to 64-69%.

This chapter shows that many chiral acrylates have been synthesised which give good to excellent chiral induction.

1.5.7 Reactive conformation of acrylate dienophiles

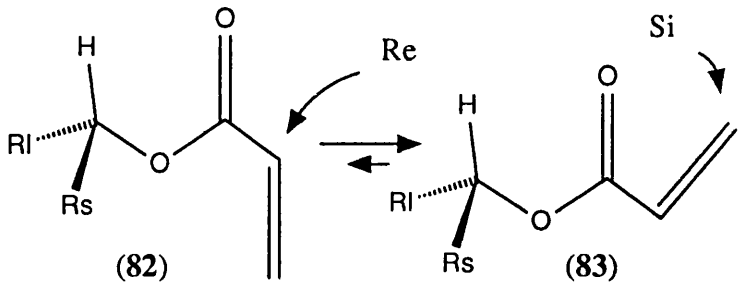
Much work has been published on the conformation of acrylate dienophiles. Early work by Hamner[44] and Walkborsky[45] was based on a model postulated by Prelog[60]. In this model the largest substituent. (R_L) **(figure 1.16)** is furthest away from the carbonyl group and the acrylate is in the S-*trans* conformation.

Fig 1.16



X-ray data for such dienophiles showed an alternative structure when R_s=H in which the the carbonyl group and H have a synperiplanar relationship (**81**). Further spectroscopic data has shown that there is an equilibrium between conformer (**82**) and (**83**) (**figure 1.17**). Conformer (**83**) has the acrylate in the S-*trans* conformation. The barrier to rotation between these conformers has been calculated to be ΔH=0.32kcalmol^{-1}. Due to this small energy difference between the two conformers, thermal Diels-Alder reactions show low chiral induction due to the presence of both conformers.

Fig 1.17

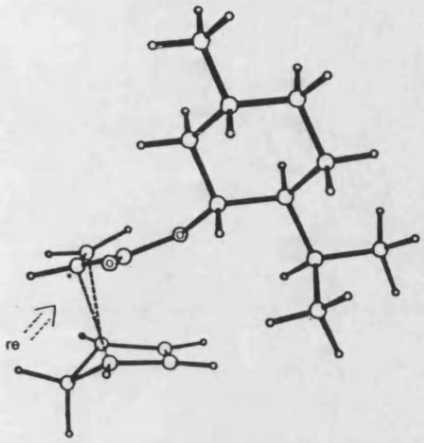


Houk et al[56,61] have published computational arguments for this lack of selectivity based on transition state models in the uncatalysed reaction. Analysis of the Lewis acid catalysed Diels-Alder reactions show that complexion increased not only endo selectivity but chiral induction as well.

X-ray and spectroscopic studies have shown that complexation of a Lewis acid occurs predominantly with the lone pair of the carbonyl oxygen orientated anti to the ester oxygen. Experimentally the cycloaddition of cyclopentadiene and (-) menthylacrylate (1.5.4) was seen to give only a modest enantiomeric excess of the 2R(+) endo and the 2S(+) exo adducts. When the reaction was catalysed with Lewis acid the 2R(+) endo and 2R(-) exo adducts are produced. It is noted that the proportion of the endo adduct is dramatically increased and the chirality of the exo product is changed on catalysis.

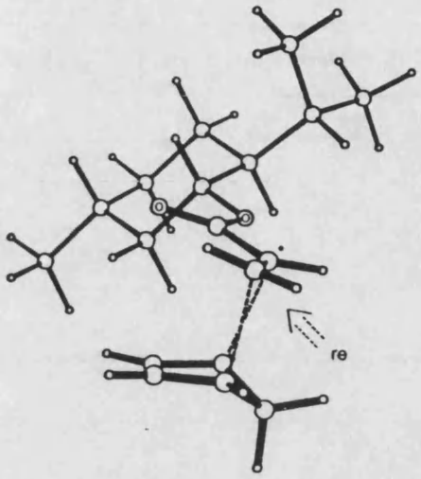
Computational analysis of the transition states for this Diels-Alder reaction are shown in **figures 1.18 and 1.19** for the *s-trans* and *s-cis* conformers respectively.

Fig. 1.18



T.S.⟶S-endo-adduct
s-trans-(−)-menthyl acrylate.

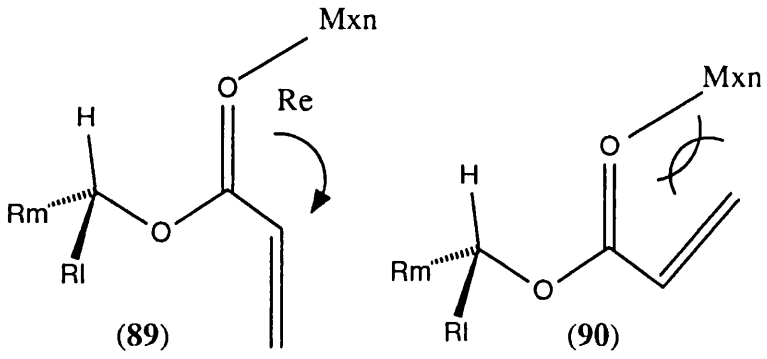
Fig. 1.19



T.S.⟶S-endo-adduct
s-cis-(−)-menthyl acrylate.

The *s-trans* conformer allows approach of the diene in an endo fashion from both *Si* and *Re* faces, affording S or R adducts respectively. The same situation is apparent for the *s-cis* conformer, **figure 1.20**. These diagrams show the preferred mode of addition is from the less hindered side near the methylene group anti to the large isopropyl group. This approach in the catalysed reaction would afford the experimentally observed R endo adduct in the *S-trans* conformer and the S endo the minor experimentally observed adduct for the *S-cis* adduct. Calculations show that the *s-trans* conformer is favoured for the catalysed reaction. In the uncatalysed reaction the *S-cis* conformer is favoured. This appears to a general rule for the type of dienophile shown in the previous section. The *s-trans* conformer is also favoured on steric grounds, **figure 1.20**, due to repulsion between the Lewis acid and the methylene hydrogens.

Fig 1.20



Enhanced endo selectivity may be explained in terms molecular orbital theory explained earlier in this chapter.

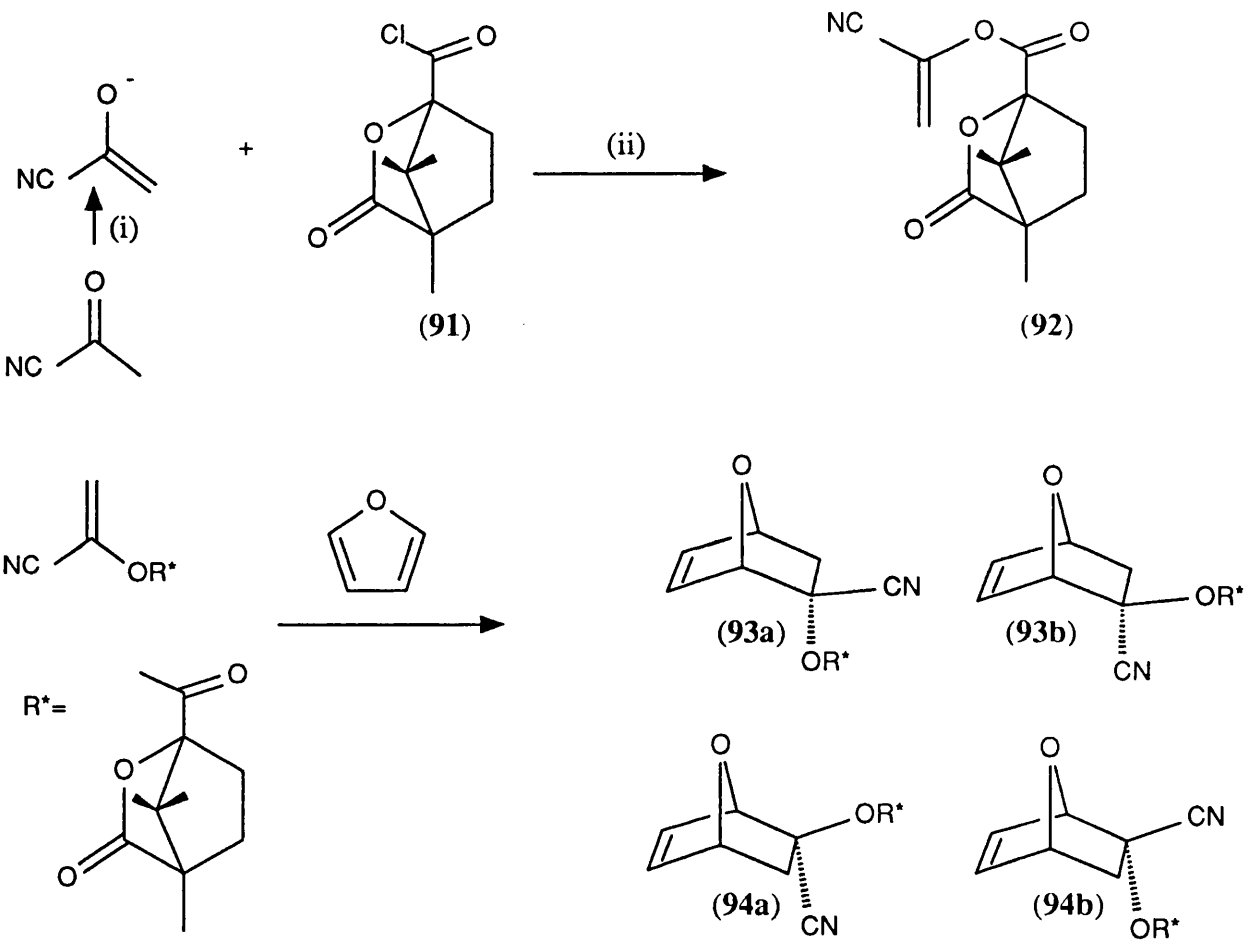
1.6.1 Chiral esters from camphanic acid

The Diels-Alder reaction of ketene equivalents and furan to produce 7-oxabicyclo [2.2.1] heptanes has been investigated for the synthesis of anthracyclins[62], muscurine derivatives[63], antibiotics[64], prostaglandins[65] and other biologically active molecules[66]. It was found that furan reacted slowly with monoactivated alkenes to afford endo, exo adducts in low yield. The reaction could be accelerated by high pressure[67] or by Lewis acid catalysis[68] however care was required when using Lewis acid catalysis to avoid polymerization of the diene.

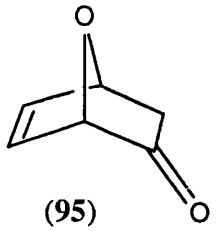
The most successful approach to these types of intermediates involved dienophiles derived from camphanic acid. Vogel et al[69]investigated the Diels-Alder

reaction of furan and the dienophile (**92**), **scheme 1.20**, which was prepared by O-acylation of oxo propiononitrile followed by reaction with (-)-camphanoyl chloride in benzene/pyridine.[70]

Scheme 1.20



Reagents: (i)Py, (ii) 20°C, 24hr

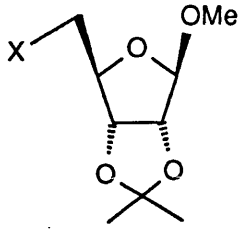


(**95**)

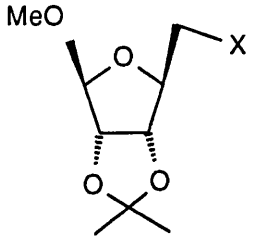
Adducts were obtained in 92% in a 4:1 endo:exo ratio. The Diels-Alder adduct (**93a**) was converted to the required enone by saponification with formalin (40% H_2CO in water) affording (+)-(1R) 7-oxabicyclo-[2.2.1]-hept-5-ene-2-one (**95**) in 96% yield. As both (+) and (-) camphanic acids are commercially available, both enantiomers of the enone are available *via* this methodology.

This type of ketene equivalent has been employed by Vogel et al in the total synthesis of (D) and (L) ribose derivatives[71] (**97** and **98**), L-alloze (**99**) and L-taloze[72] derivatives (**100**), C-ribonucleosides[73](**101**), cordycepin[74] (**102**) and lividosamine[75](**103**), **figure 1.22**

Fig. 1.22



(97)

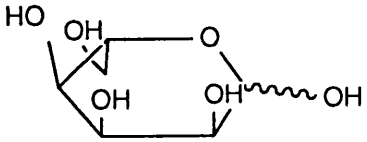


(98)

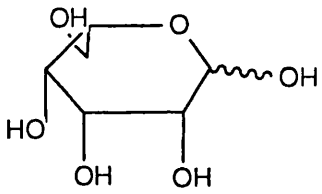
(a) X= OH

(b) X= Br

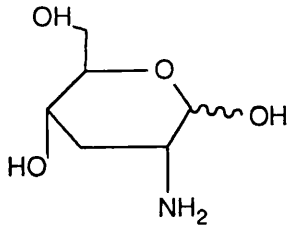
(c) X= OAc



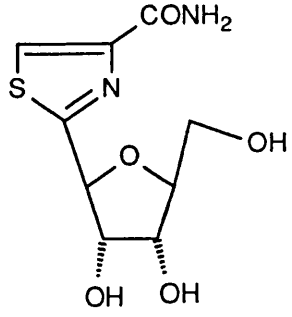
(99)



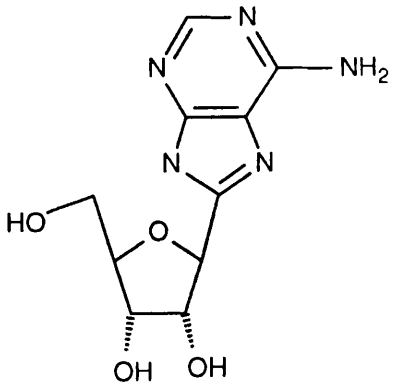
(100)



(103)



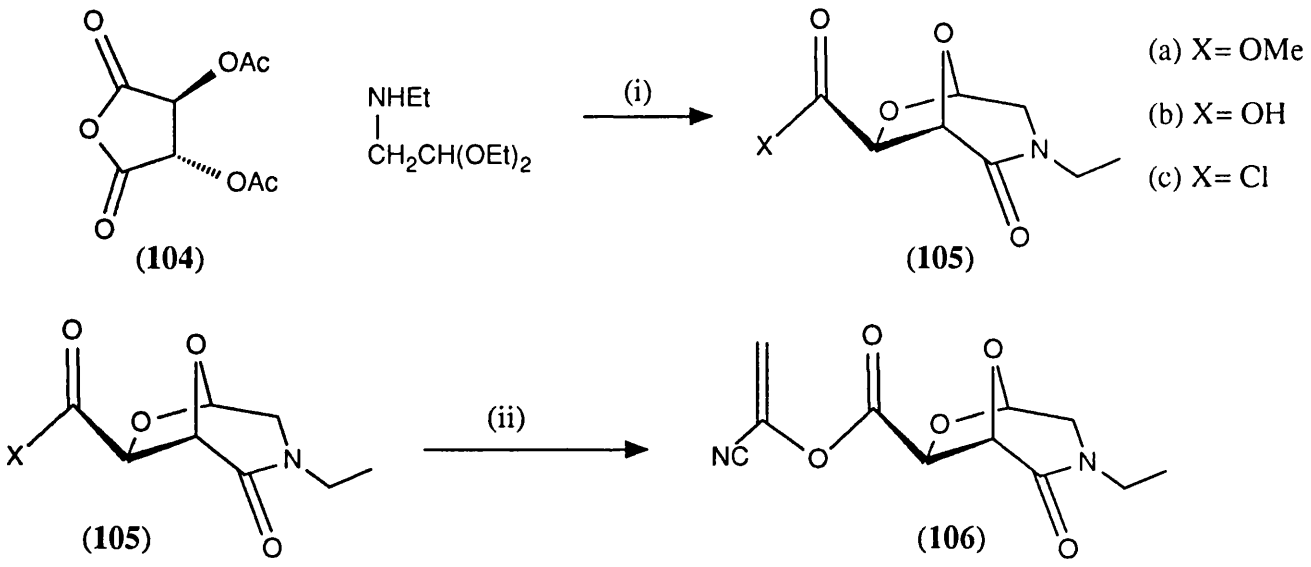
(101)



(102)

The preparation of the optically pure furan cycloadducts from 1 cyanovinyl 1-camphanate was not easy to scale up. This prompted the development of a new chiral auxiliary derived from (R,R) and (S,S) tartaric acid[76], **Scheme 1.20** shows the synthesis of the new auxiliaries (1R, 5S, 7R) and (1S, 5R, 7S)-3-alkyl-2-oxo-3-aza-6,8-dioxabicyclo[3.2.1]octane-7-carboxylic derivatives (**105**).

Scheme 1.20



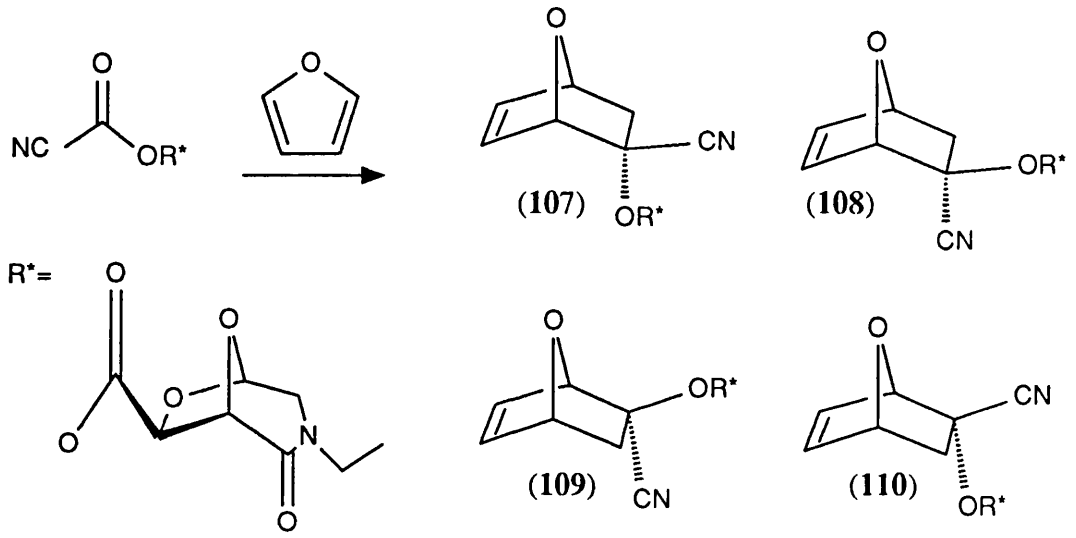
Reagents: (i) CH_2C_2, (ii) Pyruvonitrile.

Di-O-acetyl-(S,S)-tartaric anhydride (**104**) was reacted with ethylamino acetaldehyde diethyl acetal. Treatment with MeOH and $SOCl_2$ followed by H_2SO_4/SiO_2 gave (**105**) in 54% yield. Hydrolysis of (**105**) afforded acid (**105a**) which was transformed into the corresponding acyl chloride (**105c**) with SO_2Cl_2. Condensation with pyruvonitrile afforded the dienophile (**106**) in 86% yield.

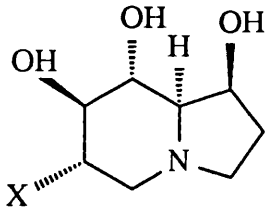
The Diels-Alder reaction of (**106**) with furan catalysed by $ZnBr_2$, at 20°C

afforded four diastereomeric adducts (**Scheme 1.21**) (**107**), 49% (**108**),31%, (**109**) and (**110**) 13%.

Scheme 1.21



Two recrystalization afforded (**107**) with greater than 99% de in 35% yield. (**108**) Was obtained from the mother liquor in 99% de. Saponification with formalin afforded the required optically active enone (**95**). Unlike the camphanate derivatives the tartaric anhydride cyanovinyl esters were amenable to scale up. The tartaric anhydride cyanovinyl esters have been employed the synthesis of 6-deoxycastanospermine (**111a**) and 6-deoxy-6-fluorocastanospermine[77] (**111b**).



(**111**)

(**111a**) X= OH

(**111b**) X= F

1.7 Chiral Sulfoxides

1.7.1 Introduction

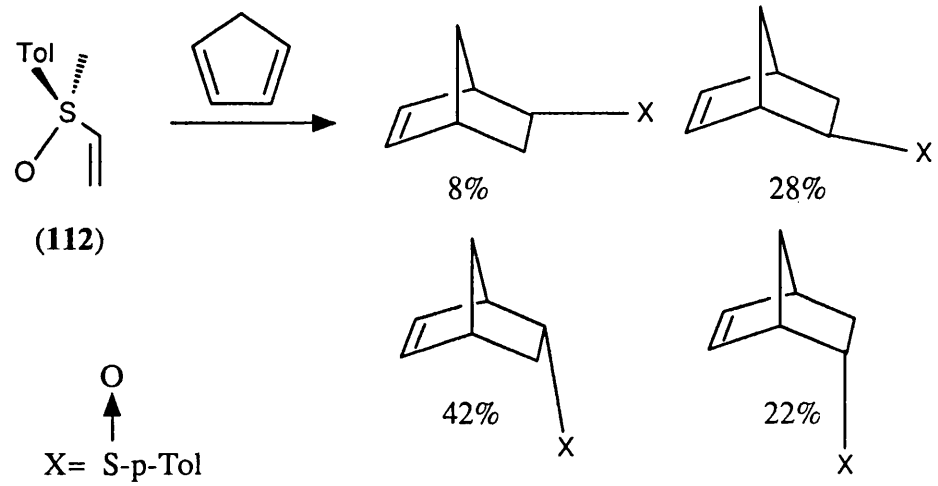
The last two chapters show that ketene equivalents have been employed successfully in the synthesis of a wide range of synthetic intermediates by combining a readily transformable latent functionality with an auxiliary that has the ability to induce high asymmetric induction. These dienophiles however suffer from practical restrictions which preclude their synthetic utility, either in multiple step synthesis of the chiral auxiliary or poor selectivity. To this end the asymmetric induction of chiral sulfoxides has been investigated. It was hoped that the relative ease of synthesis and the variety of transformations sulfoxides undergo would make them attractive dienophiles.

Diels-Alder reactions of racemic phenyl vinyl sulfoxide were reported in 1978. Subsequently asymmetric synthesis employing chiral sulfoxides has received much interest[78,79]. The Diels-Alder reactions of chiral vinyl sulfoxides was first reported by Maignan and Raphael[80] in 1983. They sought to employ (+)-(R)-p-tolyl vinyl sulfoxides in an asymmetric Diels-Alder reaction.

1.7.2 (+)-(R)-p-tolyl vinyl sulfoxide

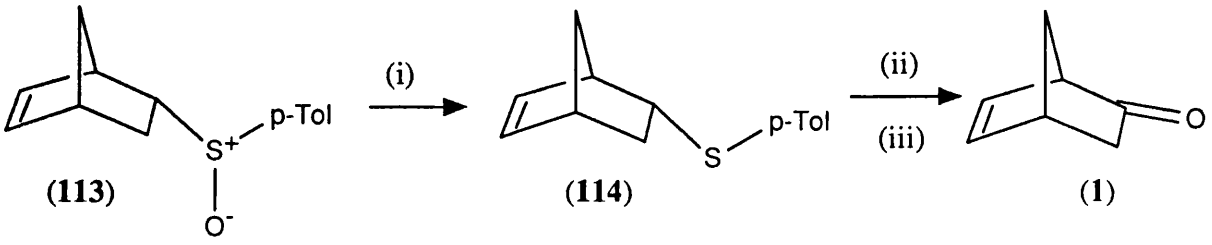
The vinyl sulfoxide (**112**)[81] was reacted with cyclopentadiene producing four isomeric products as shown in **scheme 1.22.**

Scheme 1.22



It was planned to convert the sulphoxides to a carbonyl group by a Pummerer rearrangement.[82] However this route **Scheme 1.23** was unsuccessful giving the sulphide (**114**) only. The successful route began with reduction of the sulphoxide using 2-chloro-1,3,2 benzodioxaphosphate in pyridine followed by chlorination with N chlorosuccinimide and hydrolysis with $CuCl_2$ and CuO.[83,84]

Scheme 1.23



Reagents: (i) 2-Chloro-1,3,2-benzodioxaphosphate, Py, (ii) NCS, (iii) $CuCl_2$/ CuO

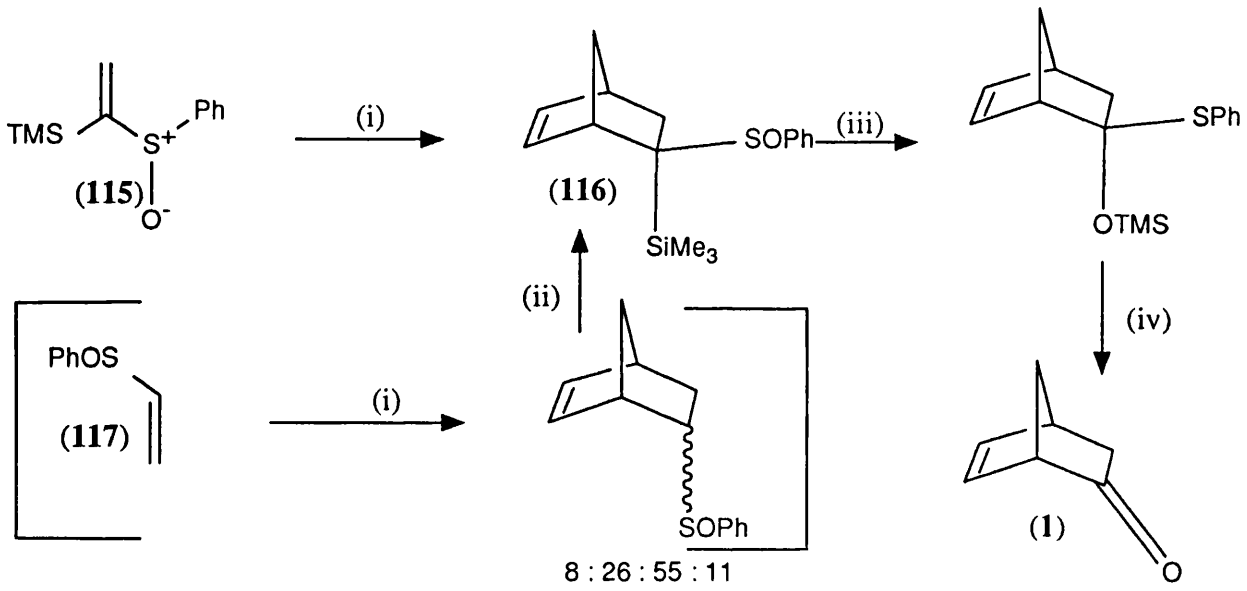
The production of four diastereomers limited its synthetic use due to the requirement of careful chromatography. Subsequent to this, much work was published on vinyl sulfoxide variants that had been designed to be more stereoselective. The

introduction of a second electronwithdrawing group, also increased the dienophiles reactivity.[85,87]

1.7.3 1-Phenyl sulphinyl-1-trimethylsilyl ethane

Based on phenyl vinyl sulfoxide[88] and vinyl sulphones as ketene surrogates, 1-phenylsuphinyl-1 trimethysilyl ethene, **Scheme 1.24**, was developed by Williams et al.[89]

Scheme 1.24

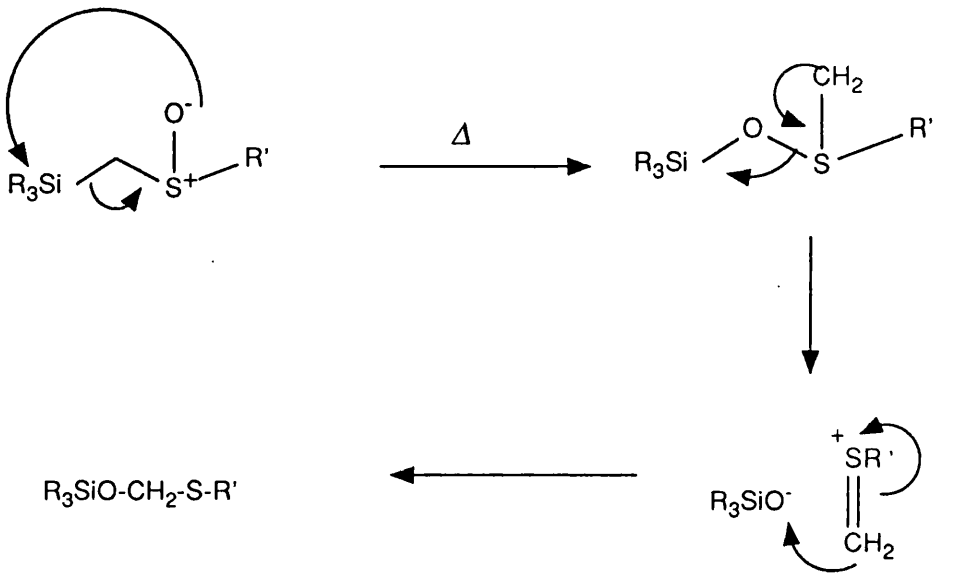


Reagents: (i) Cp, (ii) MeLi, MeSiCl, (iii) Δ (iv) H_3O^+

Hydrolysis of the ketene equivalent was achieved by lithiation of the mixture of adducts of the cycloaddition between phenyl vinyl sulfoxide and cyclopentadiene followed by silylation with TMSCl. The required ketone, was obtained after aqueous work up in 80% yield. The Diels- Alder reaction between 1 phenylsulfinyl-1-trimethylsilylethene[90,91] and cyclopentadiene in refluxing benzene gave adducts that were converted directly to the required ketone **scheme 1.25** in one pot by a facile

sila-Pummerer rearrangement.[92,93]

Scheme 1.25



Unfortunately this paper did not give any details of the selectivity of the reaction of trimethylsilyl dienophile, nor has it been prepared in optically active form . This dienophile does have the benefit of mild hydrolytic conditions.

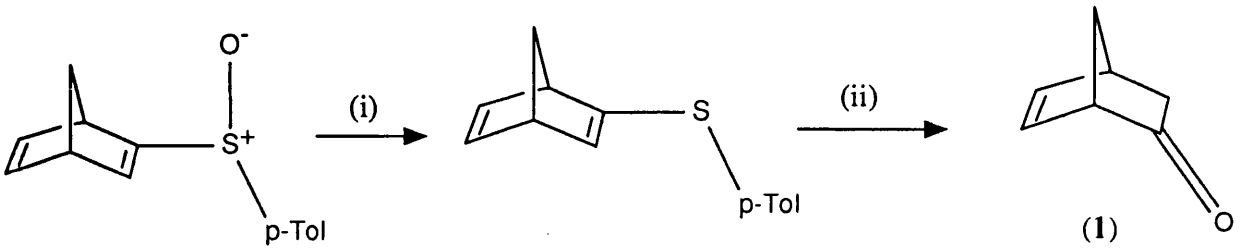
The problem of reactivity and facial selectivity still remained with these dienophiles. To restrict the products produced in the cycloaddition Miagnan[94] and et al used (R) + ethynyl *p*-tolylsulfoxide as a ketene equivalent.

1.7.4 Ethynyl-p-tolylsulfoxide

Ethynyl-*p*-tolylsulfoxide[95,96] has been found to react with cyclopentadiene under mild conditions, toluene 30°C. The two diastereomers formed (**Scheme 1.26**), were separated by flash chromatography and obtained in a 2.3:1 ratio. Both diastereomers were processed into the enantiomers of norbornenone by reduction

followed by hydrolysis and ketone (**1**) was afforded in 50% yield.

Scheme 1.26



Reagents: (i) MeSiCl3, NaI, 0°C, (ii) H_2O, TA

Although this dienophile showed good reactivity and the ability to produce both enantiomers of norborneneone under mild conditions, the selectivity of the Diels-Alder reaction was low.

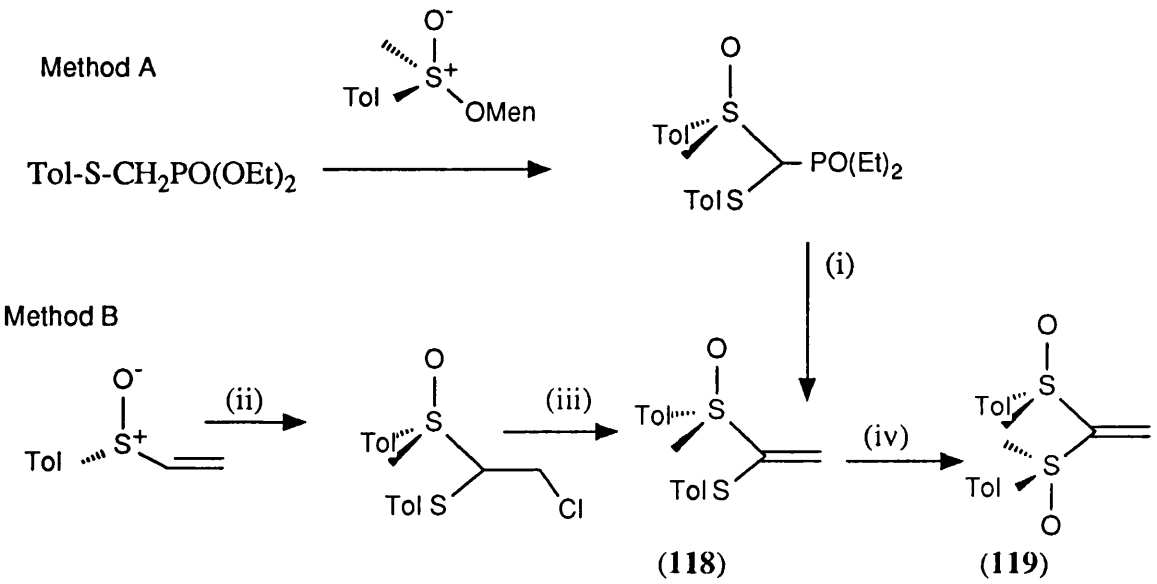
Koizumi et al had published work on the selectivity of the Diels-Alder reaction of tolylsulphinyl substituted ethenes.[86,87] (+)-(S,S)-1,1-Bis (p tolylsulfinyl)ethene[97] was found to be a potential ketene equivalent from these studies.

1.7.5 (+)(S,S)-1,1-Bis (p tolyl-sulfinyl)ethene

Two routes were used to prepare (**119**), both involving (**118**) as an intermediate. This intermediate was synthesised in 37% by a Wittig-Horner reaction between the appropriate phosphonates and paraformaldehyde, (Method A **Scheme 1.27**).

Intermediate (**118**) could also be synthesised by the addition of *p*-tolylsulphonylchloride to tolylvinylsulfoxide to form a mixture of isomers. Treatment of this mixture with triethylamine afforded the alkene (**119**), (Method B).

Scheme 1.27.



Reagents: (i) ^{n}BuLi $(CH_2O)_n$, THF, (ii) TolSCl, (iii)Et_3N, (iv) mCPBA

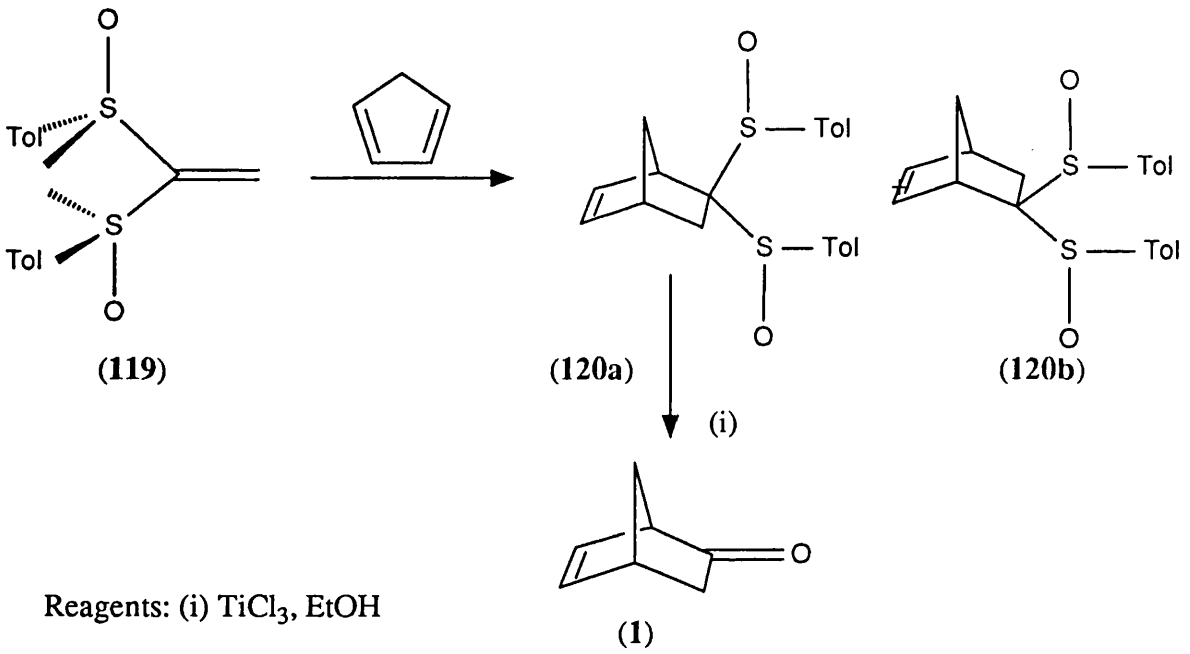
Oxidation of the intermediate with mCPBA afforded a 2:3 meso:dl mixture of diastereomers in 86% yield which were readily separated. The enantiomeric excess of the dl isomer was greater than 90%.

This example appears to be the first C_2 symmetric sulfoxide based dienophile although other C_2 symmetric reagents have been previously used in asymmetric synthesis.[99] The advantage of such a dienophile is that only two cycloadducts are possible in the Diels-Alder reaction as both faces of the dienophile are equivalent,and as such no endo exo mixtures are possible. Such a feature was thought to be very useful in the design of new ketene equivalents.

The Diels-Alder reaction of dienophile (**119**) with cyclopentadiene gave a 4:1 mixture of inseparable diastereomers (**Scheme 1.28**). The major adduct was

transformed to norborneneone (**1**) by treatment with titanium (III) chloride in acetic acid.[100] The ketone formed from this reaction was shown to be formed in 54% ee. The reaction of this dienophile with other dienes[101] and the effect of Lewis acid on diastereoselectivity[102] was referenced in this paper but was not subsequently reported.

Scheme 1.28



Reagents: (i) $TiCl_3$, EtOH

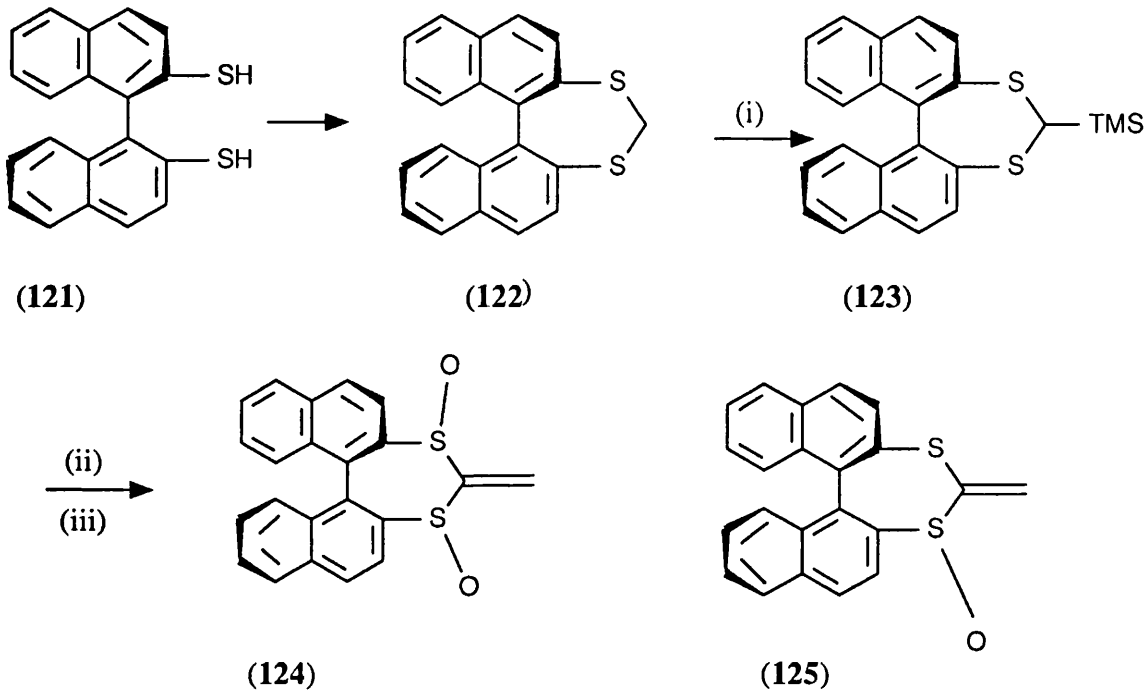
It appears that an arylsulfinyl group in the 1-possition of sulfinylethenes is not as effective at controlling stereochemistry as that inn the 2-substituted analogue[85]. The marginal increase in selectivity over ethynyl sulfoxides is negated by the inability to separate the cycloadducts.

1.7.7 1,1-Binaphthalene 2,2′ dithiol derived dienophiles

A second C_2-symmetric dienophile has been reported by DeLucci[103] on the Diels-Alder reaction of 4-methylene- 1,2,4-dinaphtho [2,1-d:1′,2-f][1,3] dithiepin using

chirality of the binaphthalene group for asymmetric induction. The synthesis of the dienophile is outlined in **scheme 1.29** starting from the dithiol.

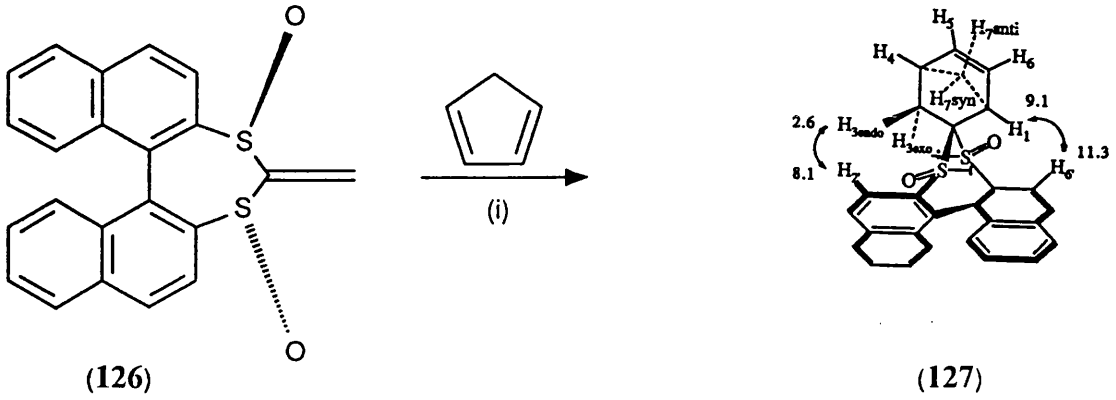
Scheme 1.29



Reagents: (i) ^{n}BuLi, MeSiCl. (ii) ^{n}BuLi, CH_2O. (iii) mCPBA, CH_2Cl_2

Cycloaddition of the moxoxide (**125**) was reported to give the four possible diasteromeric product. However, the *bis* sulfoxide gave only two diastereomers in 3:1 ratio (**scheme 1.30**) and from the stereochemistry of the major isomer (distinguished by nOe studies)it was concluded that approach of the diene to the face syn to the sulphur lone pair had occurred.[103]

Scheme 1.30



(126) (127)

Reagents: (i) $CDCL_3$, 12hr, 92%

The scope of this dienophile is limited due to the difficult asymmetric synthesis of the starting binaphthiol. However, it does show that diastereoselectivity in the Diels-Alder reaction may be based upon the preference of attack syn to the lone pair on sulfur, a concept to be utilized in the design of dienophiles explored within this thesis.

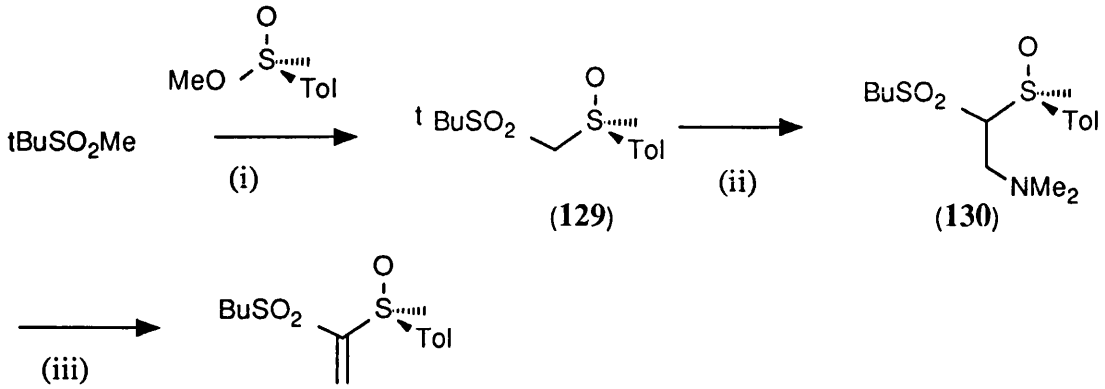
A chiral sulfoxide ketene equivalent that has high reactivity, good selectivity and mild hydrolytic conditions was reported by Carretero[104] et al. They employed (+)-(S)-1-^{t}butylsulfonyl-1-*p*-tolylsulfinylethene in an asymmetric Diels-Alder reaction.

1.7.8 (+)-(S)-1-^{t}Butylsulfonyl-1-p-tolylsulfinylethene

The chiral dienophile (**131**) was synthesised from the ^{t}butyl methyl sulfone. Deprotonation of the sulfone followed by sulfinylation with (-)-(S)-menthyl-p-toluenesulfinate gave (+)-S-^{t}butylsulfonyl-p-tolylsulfinylmethane (**129**) 98% ee.[104] Subsequent Mannich reaction of (**129**) followed by quaternization of the amine

afforded the required alkene (**131**) in 78% yield.

Scheme 1.31

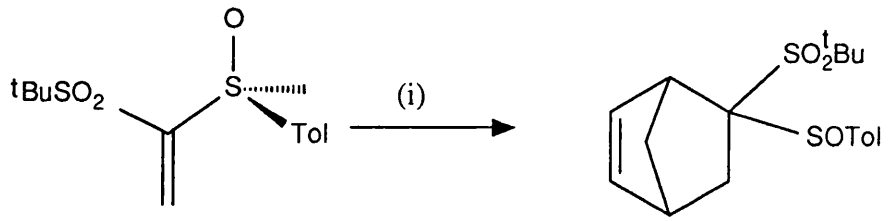


Reagents: (i) ^{n}BuLi, THF, -78°C; (ii) EtOH , $HNMe_2$, HCl, CH_2O_n

(iii) MeI, MeOH

The Diels-Alder reaction of (**131**) with cyclopentadiene was slow at room temperature and was nonselective (**Scheme 1.32**). However, Lewis acid catalysis with $Eu(fod)_3$ entry 3 (**Table 1.3**) gave good selectivity 9:1 in 70% yield. The major product was separated by flash chromatography.

Scheme 1.32



(**131**) (**132**)

Reagents: (i) cp

Table 1.3 **Effect of Lewis acid catalysis on 131**

Entry	Lewis acid	time hr	Yield %	ratio of Products
1	-	66	38	9 :23:35:23
2	$ZnBr_2$	6	68	12:- :88:-
3	$Eu(FOD)_3$	42	70	8:- :92:-
4	SiO_2	48	72	10:- :84: 6

Ratio of products determined by nmr. Stereochemistry of the cycloadducts has not been asigned.

Conversion to (+)-(1*R*,4*R*) norborneneone was achieved as before by reductive hydrolysis with $TiCl_3$.

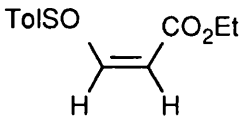
This chapter has shown that simple sulfoxides show low levels of reactivity and selectivity but that substitution at the 1 position increased reactivity and showed moderate levels of selectivity. The role of Lewis acid catalysis on the conformation of these dienophiles and how if affects selectivity has been reported.

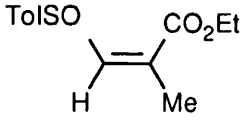
1.7.9 Stereoselectivity in vinyl sulphoxide Diels-Alder reactions

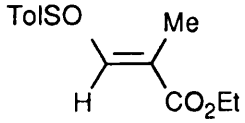
Diastereofacial selectivity has been explained by consideration of sterics. In the S-*trans* or S-*cis* conformer the less crowded side of the vinyl group is the same side as the sulfur lone pair.[85,105,106] The proportion of conformers has been thought to be influenced by substituents on the vinyl group, dipole-dipole[107], repulsions and steric hindrance felt by them. **Table 1.4** summarizes the preferred conformation for a range of vinyl sulfoxides.

Table 1.4: Ground state confomations of chiral vinyl sulpfoxides

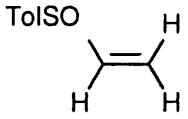
S-Trans
High diastereoselectivity

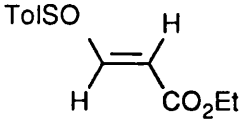




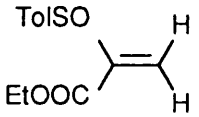


S-Trans + S-Cis
Low diastereoselectivity

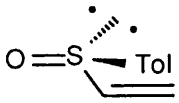




S-Cis
High diastereoselectivity



Chirality at S :

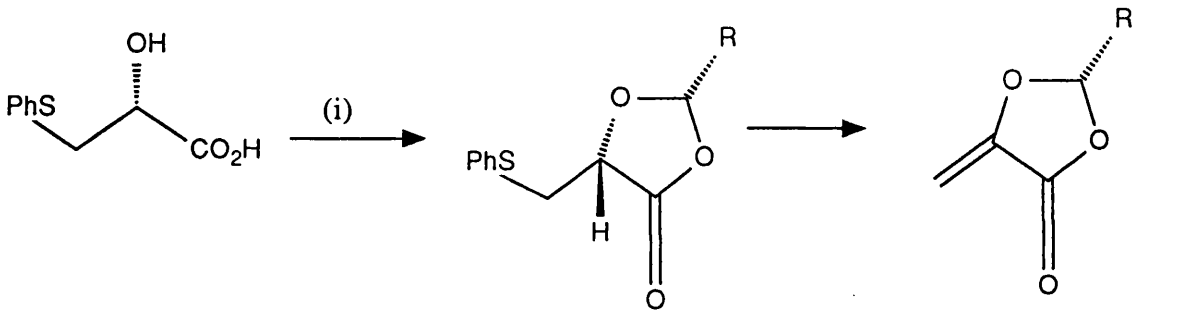


Kahn and Hehre[107] have proposed, on the basis of calculations on ground state conformations of alkyl sulfoxides, that diastereofacial selectivity arises from the electrostatic preference for a nucleophilic diene to avoid the electron-rich lone pair on sulfur even at the expense of interacting with a large bulky group. The diene attacks anti to the lone pairs and syn to the substituent. Subsequently Koizumi et al[108] published work to refute Kahn and Hehre's proposal. Koizumi's calculations incorporated alpha and beta substituents unlike Kahns simple vinyl sulfoxide which is expected to show low selectivity. These calculations for the substituted dienophiles showed that stereochemistry was primarily influenced by steric factors in ground state conformers. The stereoselectivity of the Diels-Alder reaction may best be described as attack of the diene to the S-*cis* conformer of vinyl sulphoxide and on the same side of the lone pair on sulphur. Complexation of Lewis acids to the dienophiles gives adducts with the opposite stereochemistry and this has been explained by change of the S-*cis* conformer to the S-*trans*.

1.8.0 Chiral dioxalanones

Chiral dioxalanones have been employed in numerous asymmetric syntheses[109]. Maltay[110] et al and Roush[111] studied 2-alkyl-3-acyl-5-methylene 1,3 dioxalanones (**136**) as potential ketene equivalents. **Scheme.1.33** shows the synthetic route to the new class of dienophiles.

Scheme 1.33



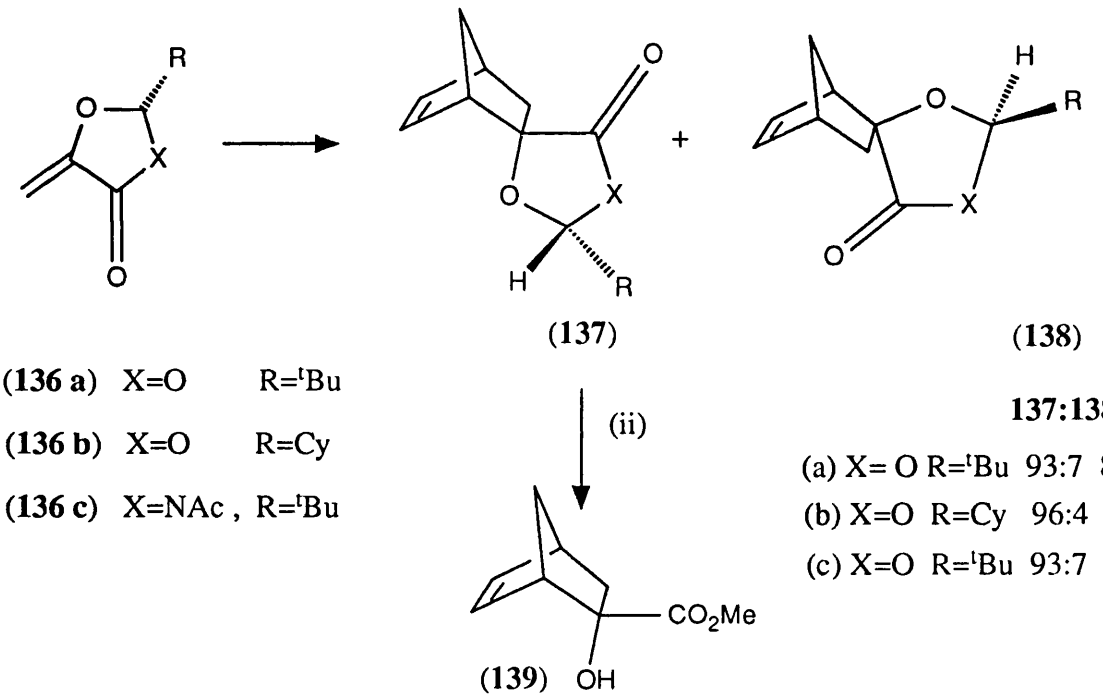
(**135 a**) R= ^{t}Bu 87% (**136 a**) 32%

(**135 b**) R= C_6H_5 72% (**136 b**) 88%

Reagents: (i) RCHO, $BF_3.Et_2O$, CH_2Cl_2, 0°C: (ii) mCPBA, CH_2Cl_2, ; (iii) DBU, CH_2Cl_2, 0°C.

The Diels-Alder reactions of (**136**) proceeded smoothly in benzene. The reactions for cyclopentadiene are summarised in **Scheme 1.34**.

Scheme 1.34



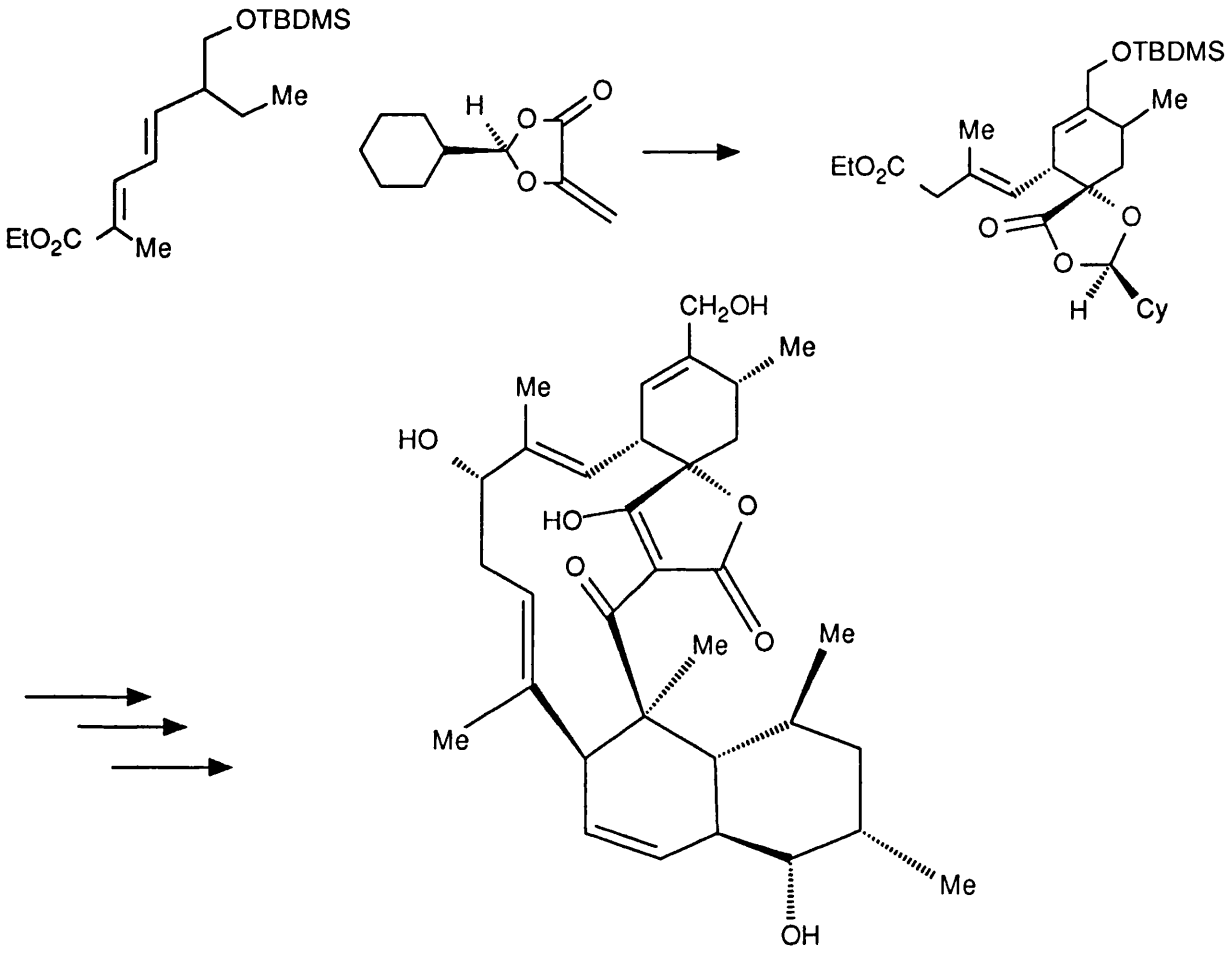
Reagents: (i) cp, C_6H_6, 65-80°C,(ii) K_2CO_3, MeOH, (for c MeOH, H_2SO_4

As seen from **scheme 1.34** the reaction proceeds with high facial selectivity (the diene approaching from the opposite side to the bulky acetal group) and high endo:exo selectivity. It is noted that high exo selectivity is observed with each of these dienophiles whereas cycloaddition with ketene equivalents usually gives only a slight preference for the endo adduct.

These Diels-Alder reactions have also been performed under Lewis acid catalysis which normally increases endo selectivity but was found to enhance exo selectivity. Reaction with cyclohexadiene was found to proceed in the same fashion. This appears to be the most selective dienophile that can act as a potential ketene equivalent with and without Lewis acid catalysis.[112]

This asymmetric induction has been exploited by Roush et al[113] (**Scheme 1.35**) in a synthesis of the top half of kyammicin in an enanteoselective fashion.

Scheme 1.35



(140)

Kinjanolide

CHAPTER TWO

RESULTS AND DISCUSSION

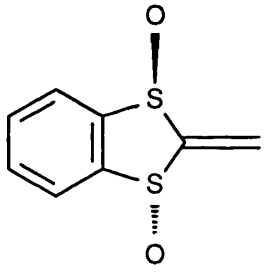
KETENE EQUIVALENTS

CHAPTER 2

Results and Discussion

2.0 Aims and Objectives

The objective of this project was to synthesise a range of novel sulphoxide based ketene equivalents and determine conditions that maximise selectivity in Diels-Alder reactions. To maximise selectivity, the dienophiles were designed with C_2 symmetry and to maximise reactivity (minimise steric hindrance), cyclic *bis* sulphoxides were incorporated.



(142)

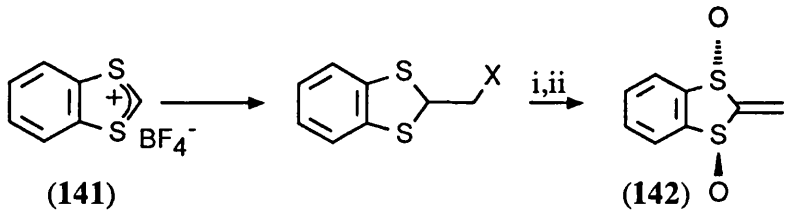
The C_2 symmetry element of the dienophile will reduce the number of different approaches that the diene may adopt, reducing the maximum number of possible products produced in the Diels-Alder reaction. It was envisaged that selectivity may be controlled due to preferential approach of the diene over either a sulphoxide oxygen or sulphur lone pair. A comparison of five and six ring dienophiles would be investigated.

Hydrolysis of the *bis* sulphoxide to a ketone would realise the potential of our dienophile to act as ketene equivalent.

2.1 Synthetic approaches towards (RS,3RS)-2-methylene-1,3-benzodithiole-1,3-dioxide (142)

The known tetrafluoroborate salt (**141**) (**Scheme 2.1**) synthesised by Nakayama et al,[114,115] appeared to be a potentially useful intermediate in the synthesis of (1RS-3RS)-2-methylene-1,3-benzodithiole-1,3-dioxide (**142**).

Scheme 2.1

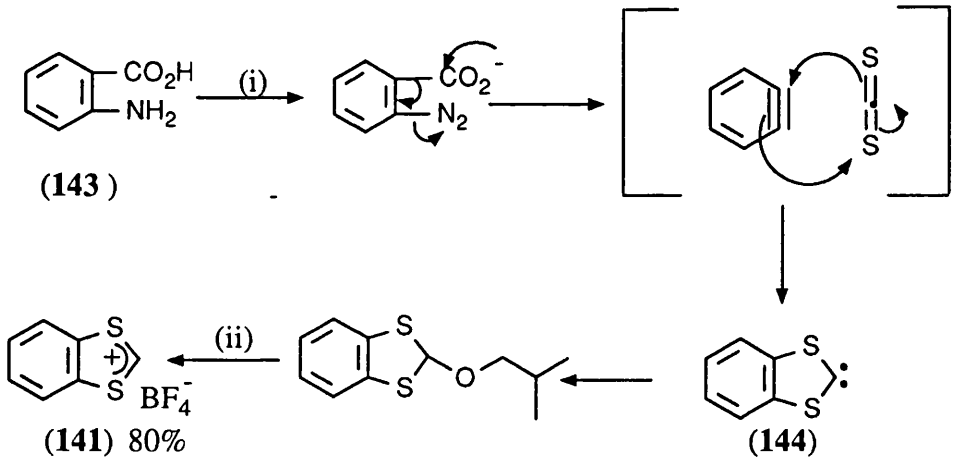


(**141**) (**142**)

Reagents: (i) Oxidation (ii) Elimination.

The tetrafluoroborate salt (**141**) was synthesised from anthranilic acid by a one pot procedure (**Scheme 2.2**). The acid (**143**) was diazotised, thermally eliminated affording benzyne which reacted with carbon disulphide, and the resultant carbene (**144**)[116] was trapped with isoamyl alcohol to afford an isoamyl ether. The ether was displaced with tetrafluoroboric acid diethyl ether complex, precipitating the air and light sensitive tetrafluoroborate salt (**141**) in 80% yield.

Scheme 2.2

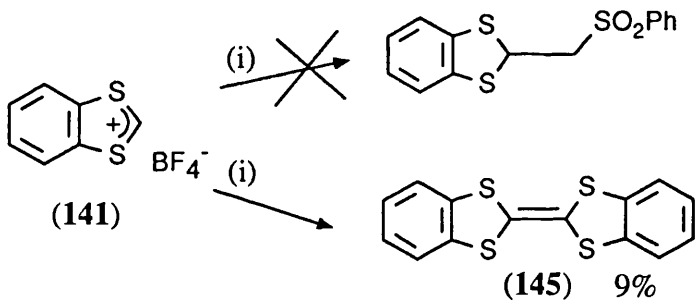


(**143**) (**141**) 80% (**144**)

Reagents: (i) $ClCH_2CH_2Cl$, p-dioxane, $C_5H_{11}ONO$ and $C_5H_{11}OH$, Δ ; (ii) $HBF_4{\cdot}Et_2O$, Et_2O.

It was hoped that the salt (**141**) would react with a suitable carbon nucleophile[115,117] which upon oxidation and elimination would afford the ketene equivalent (**142**). The carbon nucleophile would thus require a group able to stabilise an adjacent negative charge and one that could act as a good leaving group. The initial attempts to alkylate the sulphonium salt focused on the reaction with the anion of methylphenylsulphone[118] , obtained from oxidation of methylphenylsulphide with mCPBA in 30% yield. The first attempt of alkylation with sulphone (**Scheme 2.3**), by deprotonation of the sulphone with ^{n}Butyllithium in THF at -78°C afforded none of the desired product. The main product of the reaction appeared to be the known fulvene dimer[119] (**145**).

Scheme 2.3



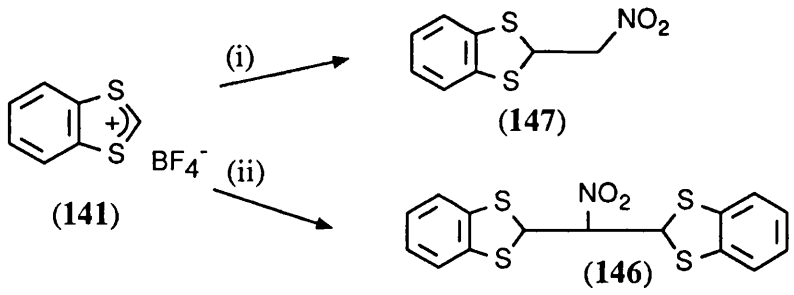
Reagents: (i) CH_3SO_2Ph, THF, ^{n}BuLi, -78^{0}C

Addition of methyllithium to (**141**) in THF at -78°C afforded a range of compounds by TLC which could not be identified. A small quantity ofthe fulvene dimer was produced in this reaction.

Another carbon nucleophile that met the above criteria was nitromethane. Nitromethane was reacted with the salt (**141**) in pyridine but none of the desired adduct (**147**) was obtained only dimer (**146**) (**Scheme 2.4**). The dimer was distinguished by

integration of the n.m.r. spectrum showing eight aromatic protons to a 2H doublet and a 1H triplet. Successful alkylation with nitromethane was achieved (**Scheme 2.4**) by deprotonation of nitromethane in THF with sodium hydride. The nitromethane adduct (**147**) was afforded in 82% yield after purification.

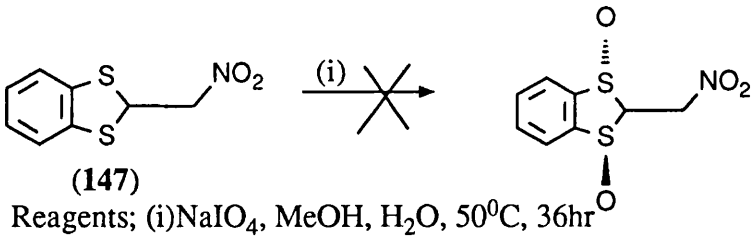
Scheme 2.4



Reagents: (i) CH_3NO_2, THF, NaH, -78^{0}C;
(ii) CH_3NO_2, Py, rt.

Elimination of nitro groups to form alkenes was known[120]. Oxidation prior to elimination was thought favourable due to the known sensitivity of the ketene thioacetal[121] (**149**). Based on previous work within the Bath laboratory, we attempted oxidation using sodium periodate but none of the required *trans* dioxide was produced, (**Scheme 2.5**). Instead a number of unidentifiable products were isolated..

Scheme 2.5



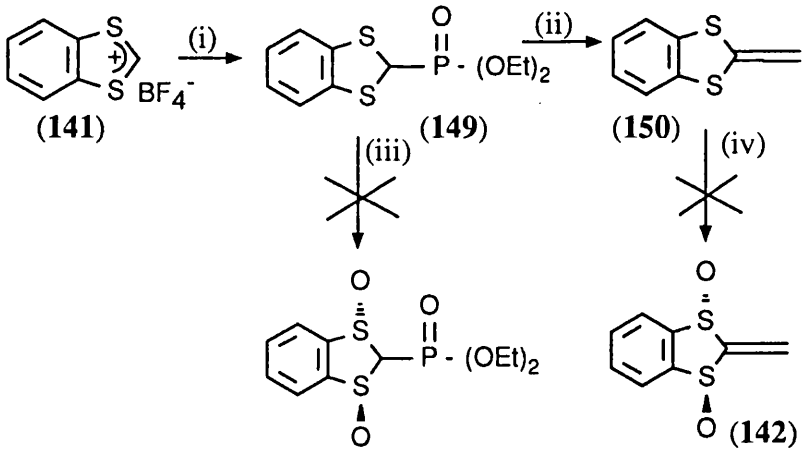
Reagents; (i)$NaIO_4$, MeOH, H_2O, 50^{0}C, 36hr

2.2 Exocyclic alkene synthesis by Wittig Horner reaction.

An alternative route to (**142**) involved a Wittig Horner reaction to introduce the exomethylene moiety. This route required the synthesis of phosphonate (**149**), a compound previously prepared by Akiba.[122] He found that (**149**) reacted with a range of aldehydes and ketones in a Wittig-Horner reaction to provide fulvenes (**150**). In our hands the Arbuzov reaction proceeded in 98% yield. Oxidation of the phosphinate (**149**) with either sodium periodate or mCPBA gave a series of unidentified compounds.

The Wittig-Horner reaction of (**149**) with paraformaldehyde proceeded in 80% yield to produce (**150**) which was oxidised immediately to prevent decomposition. Under these reactions conditions, none of the required *trans* sulphoxide was observed by proton n.m.r.

Scheme 2.6



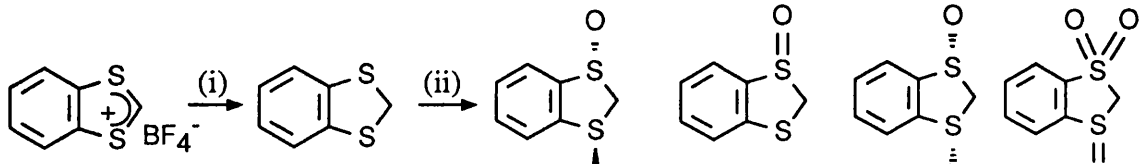
Reagents; (i) $P(OEt)_3$,NaI, CH_3CN, rt.; (ii) $HCHO_{(s)}$, ^nBuLi, THF: (iii) $NaIO_4$,MeOH, H_2O, 50°c

The inability to oxidise compounds (**147**), (**150**)and (**149**) may be due to reduced nucleopilicity of the sulphide groups by the electron withdrawing group introduced to allow facile elimination. It was decided that an alternative strategy in which oxidation of a *bis* sulphide followed by generation of an anion at the C-2 possition and addition of an electrophile would be pursued. Subsequent elimination would afford the required exocyclic alkene.

2.3 Synthesis of (1RS,3RS)-1,3-benzodithiole-1,3-dioxide (152)

Nakayama et al had reported the reduction of the tetrafluoroborate salt (**141**) with sodium borohydride[115]. In our hands the reaction proceeded in 68% yield after distillation to afford the oily 1,3-benzodithiole (**151**). Sodium periodate oxidation of (**151**), (**Scheme 2.7**) gave the *trans* dioxide (**152**) as the major product along with the monoxide (**153**), *cis* dioxide (**154**) and sulphone sulphoxide (**155**). **Table 2.1** shows the effect of temperature on the oxidation and the ratio of the products obtained.

Scheme 2.7



(**141**) (**151**) (**152**) (**153**) (**154**) (**155**)

Reagents; (i) $NaBH_4$, THF, 0°C, 2 hr; (ii) $NaIO_4$, MeOH, H_2O, 50°C, 36hr.

Table 2.1: Effect of temperature on periodate oxidation of (151)

Entry	Conditions	Time	Ratio			
			(152)	(153)	(154)	(155)
1	rt	36hr	6	1	1	4
2	50^0C	36hr	6	1.6	1	1

The *trans* sulphoxide (**152**) was distinguished from the *cis* diastereomer by proton n.m.r. As the *trans* sulphoxide has C_2 symmetry the protons at C-2 appear as a 2H singlet. The C-2 protons of the other oxidation products are not magnetically equivalent and appear as an AB system.

The rate of over-oxidation of the dioxides (**152**),(**154**) to the sulphone sulphoxide (**155**) was studied by taking the two compounds and separately subjecting them to normal oxidation conditions. After twenty four hours since twice as much sulphone sulphoxide was produced from the *cis* dioxide as for the *trans* dioxide, it was concluded that the rate of oxidation of the *cis* dioxide was found to be roughly twice as fast as that for the *trans* isomer. This allowed optimization of the reaction conditions to produce the maximum yield of the *trans* dioxide with the minimum production of sulphone sulphoxide. It also showed that different ratios of *cis* and *trans* dioxides could be expected depending on the extent of over-oxidation.

2.3 Anion reactions of 1,3-Benzodithiole-1,3-dioxide (152)

The crystalline *trans* dioxide (**152**) could now be used as a nucleophile after deprotonation of a proton at C-2. Initial attempts to introduce the required exocyclic methylene were focused on hydroxymethylation. **Table 2.2** summarises the reaction conditions investigated.

Table 2.2: Reaction conditions for hydroxymethylation of (152)

Entry	Base	Solvent	Formaldehyde Source	Product
1	BuLi	THF	Paraformaldehyde[a]	b
2	LDA	THF	Paraformaldehyde[a]	**(156)**
	LDA	THF	Formaldehyde[c]	**(156)**
3	K_2CO_3	H_2O	Formaldehyde[d]	**(156)**
5	K_2CO_3	THF	"	**(156)**
6	K_2CO_3	^{t}BuOK	"	**(156)**
7	K_2CO_3	DMF	"	**(156)**
8	K_2CO_3	THF/Mol sieves	"	**(156)**
9	K_2CO_3	^{t}BuOH/Mol sieves	"	**(156)**
10	K_2CO_3	MeOH	"	**(157)**

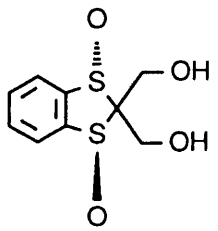
In each case one equivalent of formaldehyde was used and starting material recovered as well as product.

(a) Paraformaldehyde was predried in a NORMAG tube over P_2O_5 at 100°C for 10 hr.

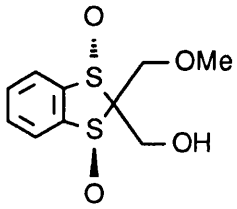
(b) Multiple spots unidentified by Proton n.m.r.

(c) Formaldehyde gas was generated by heating predried paraformaldehyde (a) at 180° and passing the gas to the reaction vessel.

(d) Formalin.



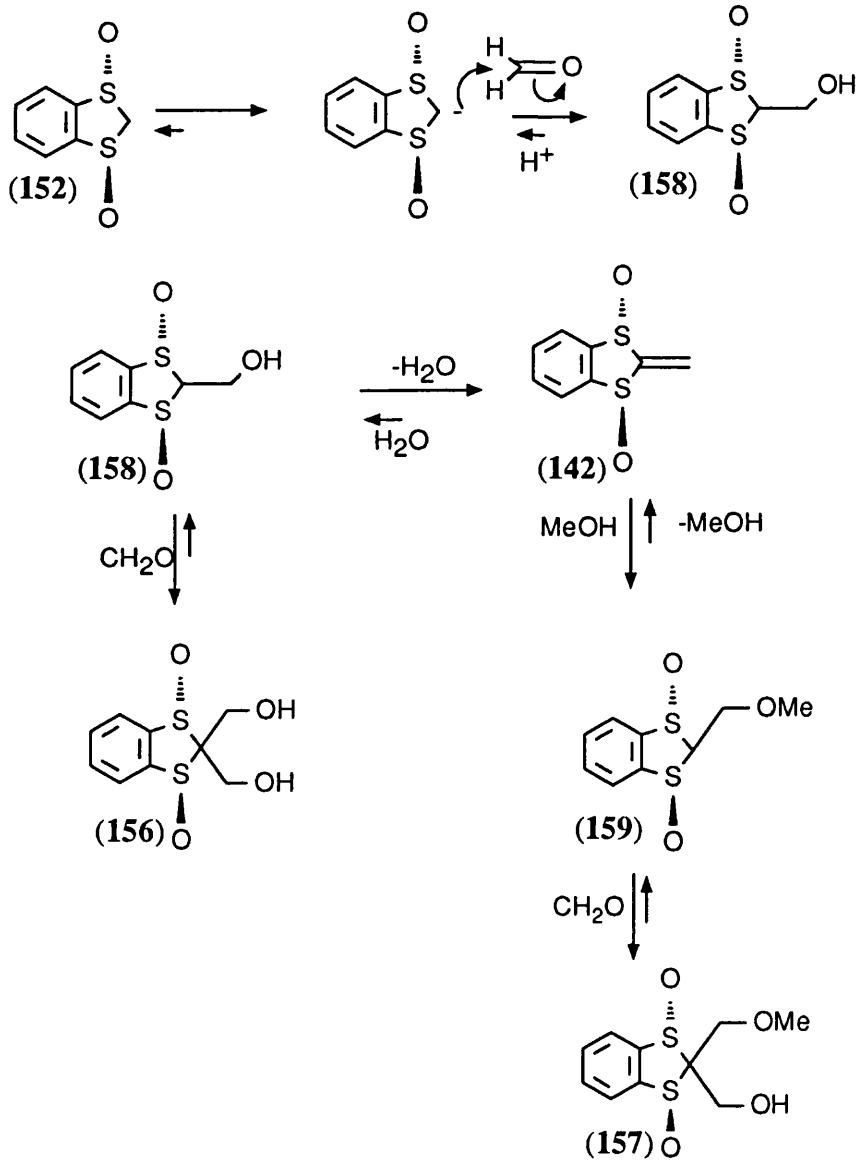
(156)



(157)

The formation of the methyl ether (**157**) (**scheme 2.8**), when the reaction was conducted in methanol suggested that the desired elimination had occurred to give (**142**). Under basic and protic conditions this intermediate underwent further addition reactions.

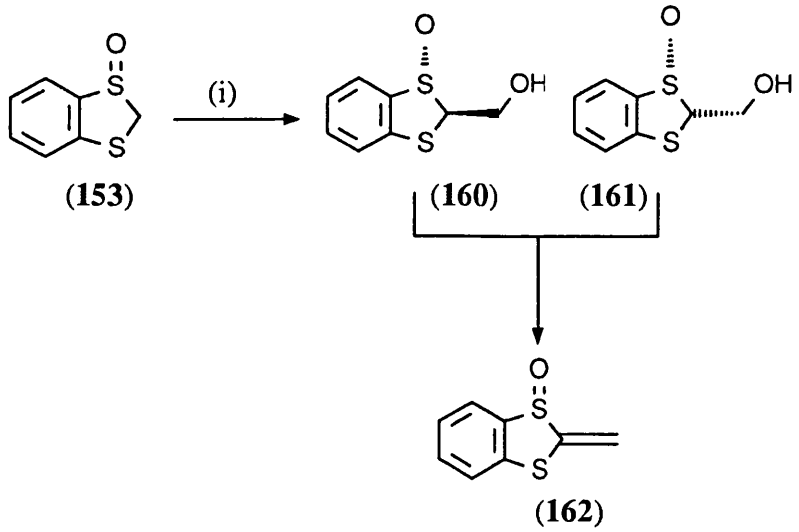
Scheme 2.8



Entries 2-7 (**Table 2.2**) show that the preferred product of reaction was the diol (**156**). Assuming that the equilibria shown in scheme 2.8 were operative, attempts were made to push the equilibrium over to (**142**) by conducting the reaction in aprotic solvent and by removing water (entries 8, 9).[123] However, this was not found to be successful.

Unable to prevent the second deprotonation it was decided to attempt hydroxymethylation of the monoxide (**153**) which should be more stable due to lower level of activation with only one sulphoxide. Hydroxymethylation of the monoxide (**Scheme 2.9**) was found to afford a 1:1 mixture of the two diastereomers (**160**) and (**161**).

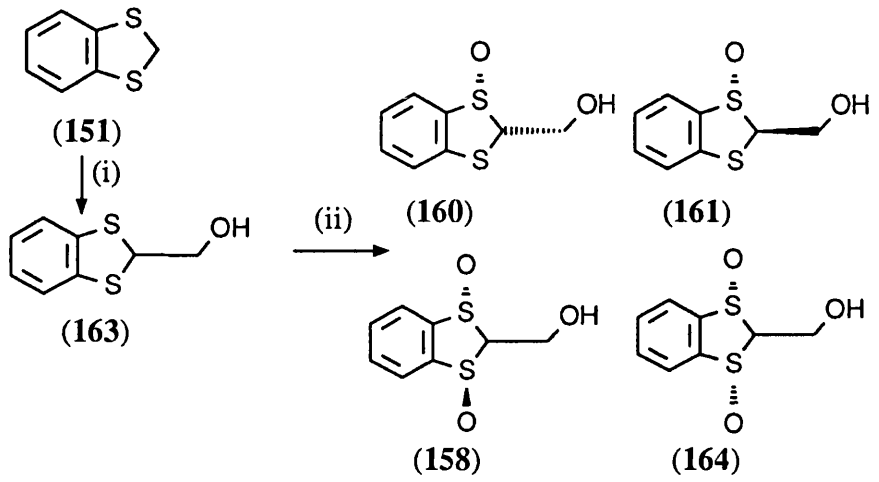
Scheme 2.9



Reagents; (i) ^{n}BuLi, $(CH_2O)_n$, THF, -78°C.

In the same way reactions with the non-oxidised derivative, bissulphide (**151**) under the same conditions (**Scheme 2.10**) afforded the hydroxymethyl adduct (**163**) in 80% yield. This was oxidised under a variety of conditions.

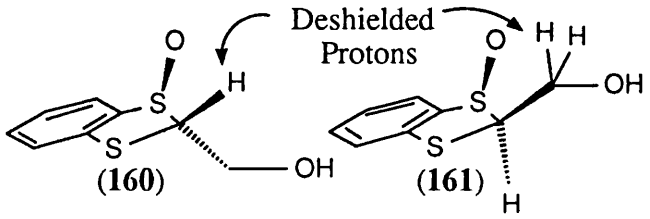
Scheme 2.10



Reagents: (i) CH_2O,THF, ^nBuLi, -78^0C; (ii) $NaIO_4$, MeOH, H_2O.

It was found that the rate of the second oxidation of the second sulphide was much slower than the first. Although substituted 1,3 benzodithioles have been oxidised in the past no data for a *bis* sulphoxide was found. The stereochemical assignments of (**160**) and (**161**) are based on the observations that protons *cis* to sulphoxides suffer greater deshielding compared to protons that are *trans* to sulphoxides (**fig 2.1**). [124]

Fig 2.1

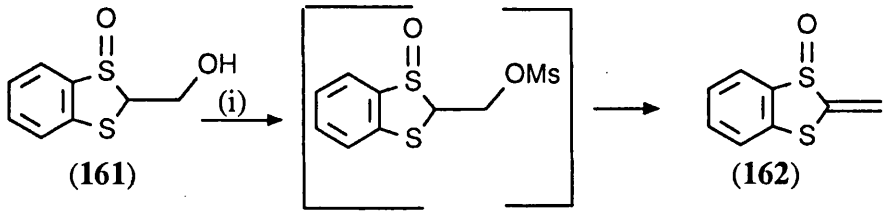


Although it was now possible to produce the required *trans* dioxide (**158**), albeit in low yield, attempts were made to utilise the monoxide (**161**) in the synthesis

of (**142**).

Mesylation[125] of the *trans* monoxide diastereomer gave the required product (**162**) (**Scheme 2.11**) in 80% yield, presumably *via* elimination of the mesylate intermediate.

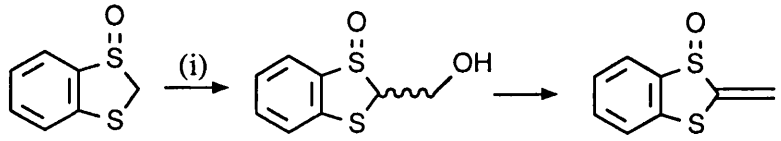
Scheme 2.11



Reagents: (i) MsCl, Et_3N, CH_2Cl_2, 0°C.

The same product was also obtained by hydroxylation of (**153**), which again gave a 1:1 ratio of diastereomers, followed by the same treatment with methane sulphonyl chloride (**scheme 2.12**).

Scheme 2.12

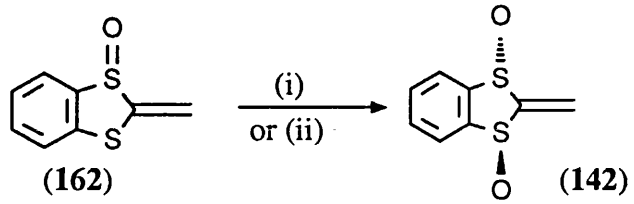


Reagents; (i) ^nBuLi, $(CH_2O)_n$, THF, -78°C.

Attepted sulphoxide oxidation of (**162**) with either sodium periodate or sodium perborate[126] gave a range of products by TLC which could not be identified by

proton n.m.r.

Scheme 2.13

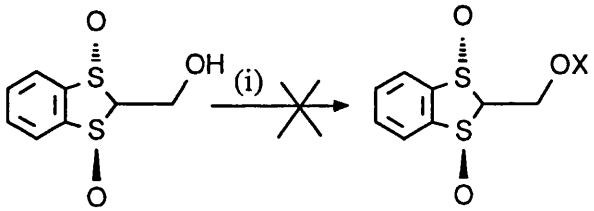


(162) **(142)**

Reagents; (i) $NaIO_4$, MeOH, H_2O, 50°C; (ii) $NaBO_4.6H_2O$ MeOH, H_2O.

The unsuccessful nature of these oxidations led us to consider dehydration of the *trans* dioxide hydroxymethyl compound (**158**). Both mesylation and tosylation were attempted, but neither the mesylate nor tosylate was isolated (**scheme 2.14**). The eliminated product of these reactions could not be detected either.

Scheme 2.14



(158) **(165)** X= Ts
(166) X= Ms

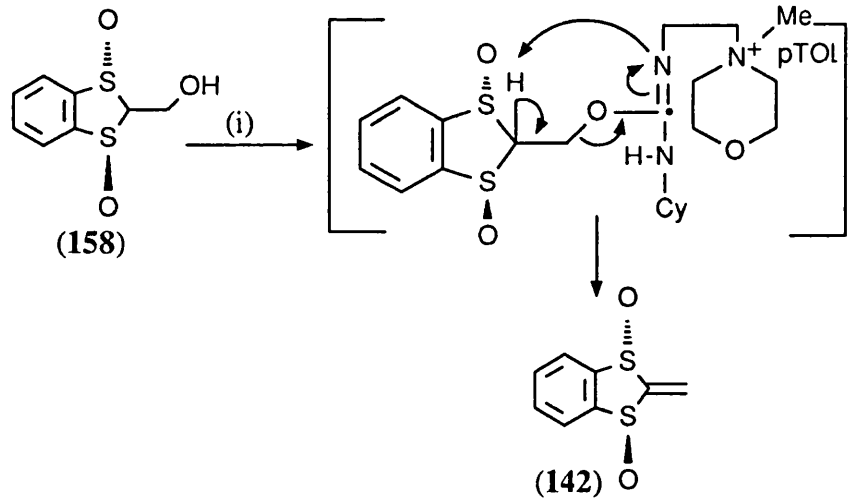
Reagents; (i) TsCl or MsCl, Et_3N, THF, 0°C.

A report in the literature by J.A. Marshal[127] on α- methylene synthesis indicated that in the cases where the dehydration of a hydroxymethyl group to an alkene was found to be difficult by existing methodology i.e. tosylation or mesylation, the dehydrating reagents 1-cyclohexyl-3- (-2-morpholinoethyl) carbodiimide metho-p-toluenesulphonate (**167**), appeared to be an attractive alternative.

In our hands the dehydration (**Scheme 2.15**) afforded a single compound by TLC. Crude proton n.m.r. of the reaction mixture showed the presence of the required alkene along with the urea by-product of the reaction.

Unfortunately under these reaction conditions the compound could not be isolated pure by either filtration of the urea product and flash chromatography eluting with isopropanol and methylene chloride or by removing the copper (II) chloride with $NH_4^+OH^-$ followed aqueous wash. In each case decomposition resulted upon concentration.

Scheme 2.15



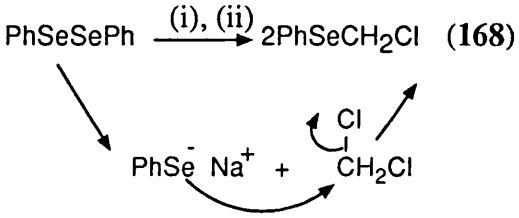
Reagents: (i) 1-Cyclohexyl-3-(2-morpholino-ethyl)carbodiimide-metho-p-toluenesulphonate, CH_3CN,$CuCl_2$.

2.4 Other Anion reactions

A review of α olefin synthesis showed that alkylation with a sulphide or selenium reagent followed by oxidation to the sulphoxide or selenoxide followed by

elimination[128] would afforde exo cyclic olefins. The appropriate selenium reagent would be chloroselenophenylmethane (**168**) which was synthesized (**Scheme 2.16**) by a method developed by A.L.J. Beckwith[128]. In this reaction diphenyldiselenide was dissolved in ethanol, reduced by 2.6 equivalents of sodium borohydride, the solution transferred to dry methylene chloride and refluxed for one hour.

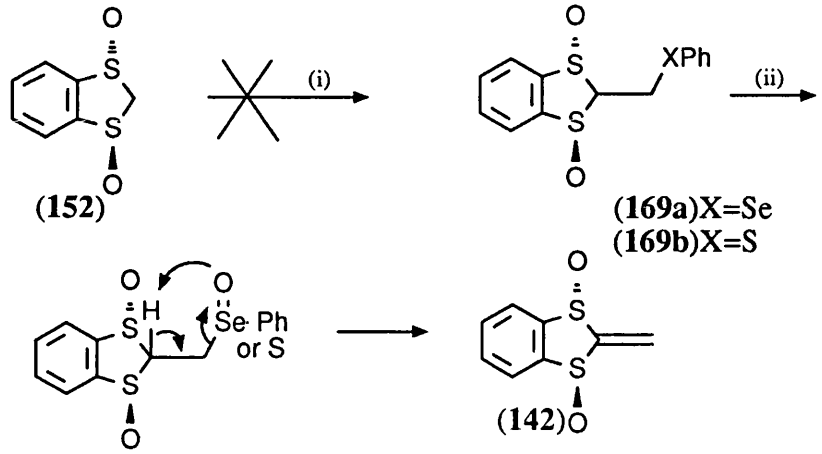
Scheme 2.16



Reagents; (i) $NaBH_4$, EtOH, (ii) CH_2Cl_2, reflux

It was hoped that alkylation with this selenide or the commercially available sulphide would afford intermediates (**169a**) and (**169b**),(**Scheme 2.17**), subsequent mCPBA oxidation would allow β elimination. However in both cases the alkylated products (**169a**) and (**169b**) could not be isolated. Complicated proton n.m.r. precluded identification; the C-2 proton normally distinguish with ease in the mono alkylated products could not be seen, possibly indicating *bis* alkylation.

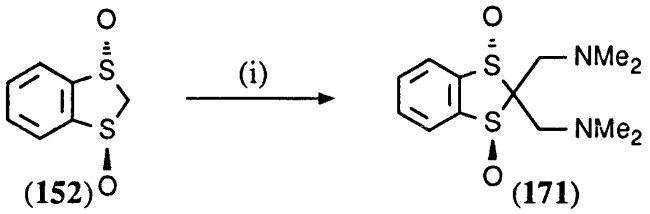
Scheme 2.17



Reagents; (i) $PhSeCH_2Cl$ (or $PhSCH_2Cl$), KHMDA, THF,-78°C
(ii) mCPBA, CH_2Cl_2, 0°C

Eschenmoser has employed N,N', dimethylmethylene ammonium iodide (**170**) (Eshenmoser's salt)[129] in the synthesis of exocyclic alkenes for the synthesis of vernolepin. The reaction of this salt (**Scheme 2.18**) with the anion of racemic 1,3-benzodithiole-1,3-dioxide (**152**) was carried out. As before deprotonation with a range of bases and solvents (**Table 2.4**) gave the characteristic yellow anion which upon treatment with (**170**) afforded the *bis* alkylated adduct along with starting material.

Scheme 2.18



Reagents: (i) $CH_2=\overset{+}{N}Me_2\overset{-}{I}$ (**170**), base, THF.

Table 2.4: **Effect of base on product ratio with Eschenmosers salt**.

Entry	Conditions	Products
1	LDA/THF	Bis amine (**171**) + (**152**)
2	LDA/THF, Acid wash	(**152**) + (**172**)mono Alkene (**142**)
3	K_2CO_3/THF	(**171**)
4	LTMP/THF	(**171**) + (**152**)
5	HMDS/THF/DMF	(**171**) + (**152**)

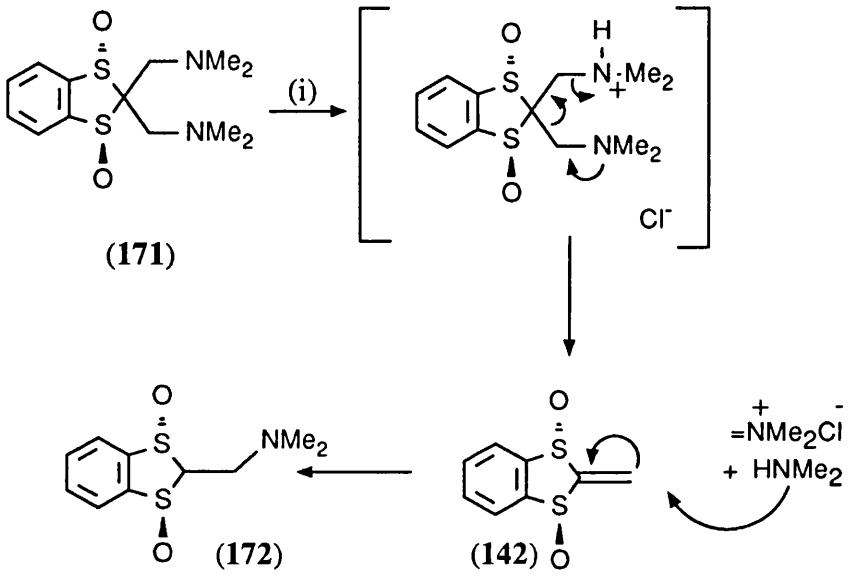
Although small and variable amounts of both the alkene (**142**) and the mono alkylated (**172**) adduct had been produced in these reactions the yields precluded the synthetic utility of this route.

2.4 Synthesis of exocyclic alkenes by Mannich reactions

The Mannich reaction has been employed by Grieco[130] and others[131] to introduce exocyclic methylene groups α- to an electron withdrawing substituent.

Typically these reactions were performed with an ethanolic solution of dimethylamine (**Scheme 2.19**). It was discovered that under these conditions the *bis* dimethylamine adduct was afforded in 91%. The *bis* dimethylamine adduct (**171**) could be converted to the monoamine adduct by prolonged stirring in dilute aqueos acid in quantatative yield.

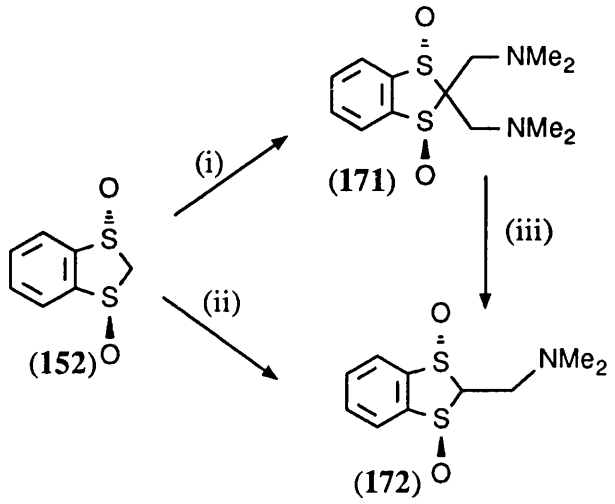
Scheme 2.19.



Reagents: (i) HCl

This indicated that if the Mannich reaction was performed under aqueous conditions the monoamine (**172**) would be formed directly. Indeed reaction with aqueous dimethylamine and aqueous formaldehyde (formalin) under the same conditions gave the required momoamine as expected in 87% yield (**scheme 2.20**).

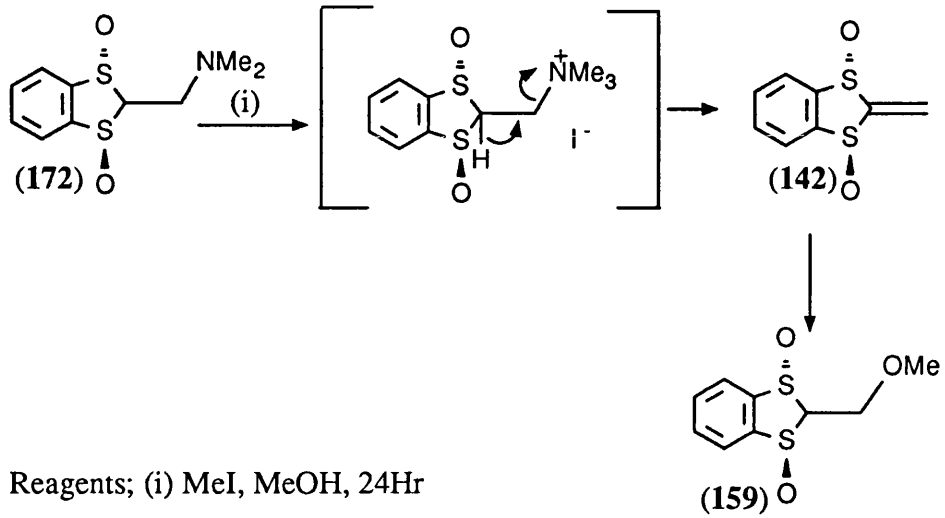
Scheme 2.20



Reagents; EtOH, $HNMe_2$(37% sol^n in EtOH)
HCl (conc^n), 50°C, 36Hr; (ii) H_2O, $HNMe_2$ (40%sol$^n{}_{aq}$)
HCl (conc^n), 50°C, 36Hr; (iii) HCl (dil), H_2O.

The amine was found to be highly crystalline and the X-ray structure is shown in appendix 2. The amine was readily eliminated to the required ketene thioacetal (**142**) with methyl iodide in dichloromethane (**Scheme 2.21**). Purification from the trimethylammonium iodide eliminated in the reaction proved to be difficult and the amine (**172**) was used as a convenient place to store the alkene. Quaternization and elimination was found to be quantitative and could be performed *in situ*. The presence of the ammonium salt had no effect on the diastereoselectivity of the Diels-Alder reaction.

Scheme 2.21



Reagents; (i) MeI, MeOH, 24Hr

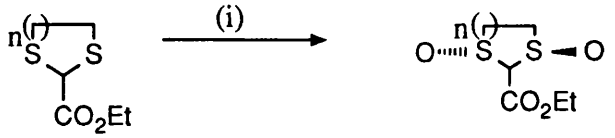
If methanol was used as the solvent for quaternisation, the methoxymethyl adduct (**158**) was obtained in 89% yield. Therefore the reaction was performed in neat iodomethane.

With the first potential dienophile in hand the two other unsaturated cyclic alkenes were sought.

2.5 Synthesis of (1RS,3RS)-2-methylene-1,3-dithiane and 1,3-ditholane dioxide

Both the five membered dithiolane and six membered dithiane rings were commercially available in the form of the 2-carboxylate ethyl ester (**173**) and (**174**). Initial synthetic routes envisaged oxidation[132] of these esters to the *trans bis* sulphoxides (**175**) and (**176**) (**Scheme 2.22**),
followed by lithium aluminium hydride reduction of the ester to the hydroxymethyl compounds (**177**) and (**178**) which could be dehydrated to give the required alkenes.

Scheme 2.22



(**173**) n=1
(**174**) n=2

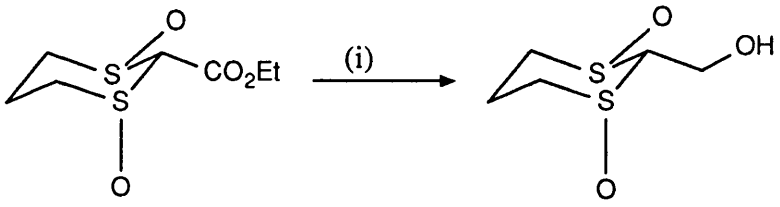
(**175**) n=1 not isolated
(**176**) n=2

Reagents: (i) $NaIO_4$, H_2O, MeOH, 50°C, 36Hr.

However attempted oxidation of (**173**) with either $NaIO_4$ (or mCPBA) resulted only in decomposition. Oxidation of (**174**) occurred in moderate yield (50%) using mCPBA; periodate again caused decomposition. Asymmetric oxidations of (**174**) have been performed by kagan[133] and Page[134] as well as others at Bath[135].

Reduction of the six membered dithiane dioxide ester (**176**) was attempted with lithium aluminium hydride (**Scheme 2.23**). Since only starting material was recovered a range of other reducing reagents were investigated, the results of which are summarised in **table 2.5**

Scheme 2.23



(**176**) (**177**)

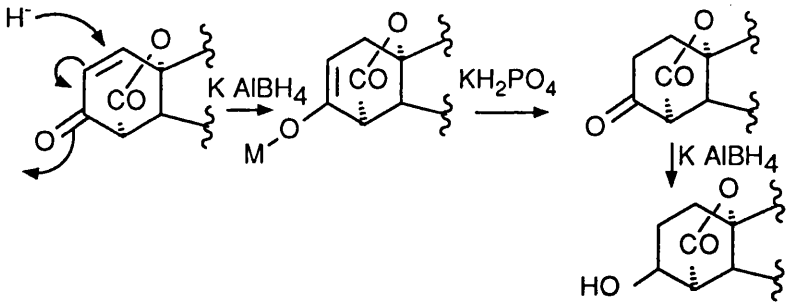
Reagent: (i) see table 2.5

Table 2.5

Entry	Conditions	Ref	Results
1	LAH, THF, -78°C	134	Starting Material
2	DiBAL, TOL, -78°C	135	Starting Material
3	REDAL, TOL, -78°C	136	Starting Material
4	K Selectride, KH_2PO_4 THF	137	Starting Material
5	AlH_3, THF	138	Starting Material
6	$Ca(BH_4)_2$,THF, 0°C	139/40	Starting Material
7	$Li(BH_4)$, MeOH 0°C -50°C	141	Starting Material

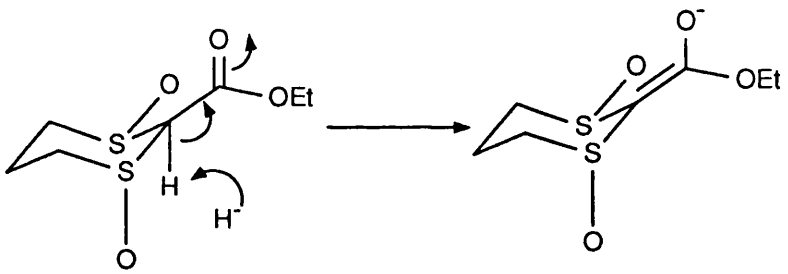
As seen in **table 2.5**, all reducing reagents tried failed to give the required alcohol. Entries 1,2 and 3 appeared, by TLC, to form a baseline material which reformed the ester upon aqueous work up. This indicated that they had acted as bases and had removed the C-2 proton rather than acting as a nucleophile (**Scheme 2.23**). The C-2 proton is very acidic and deprotonation would afford an enolate. Such a species would be expected to be unreactive towards addition of H^- (**scheme 2.24**). A report by Turner et al on the selective reduction of 3-keto gibberellin acids with K selectride and KH_2PO_4 buffer[137] (**Figure 2.2**) circumvented the problem of enolate formation by reprotonation of the enol borate intermediate with KH_2PO_4.

Fig 2.2: Protonation of enolborate with KH_2PO_4



However in our hands no reduction occurred. Entry 6 using $Ca(BH_4)_2$ was investigated due to a publication by H.C.Brown[140] advocating the use of $Ca(BH_4)_2$ as a superior reducing reagent which could be used in protic solvents. Thus, if enolate formation occurred it could be reprotonated under the reaction conditions. $Ca(BH_4)_2$ may be produced *in situ* or by the reaction of calcium chloride with two equivalents of sodium borohyride in THF. However, with the dithiane ester (**176**) as a substrate, no reaction was observed.

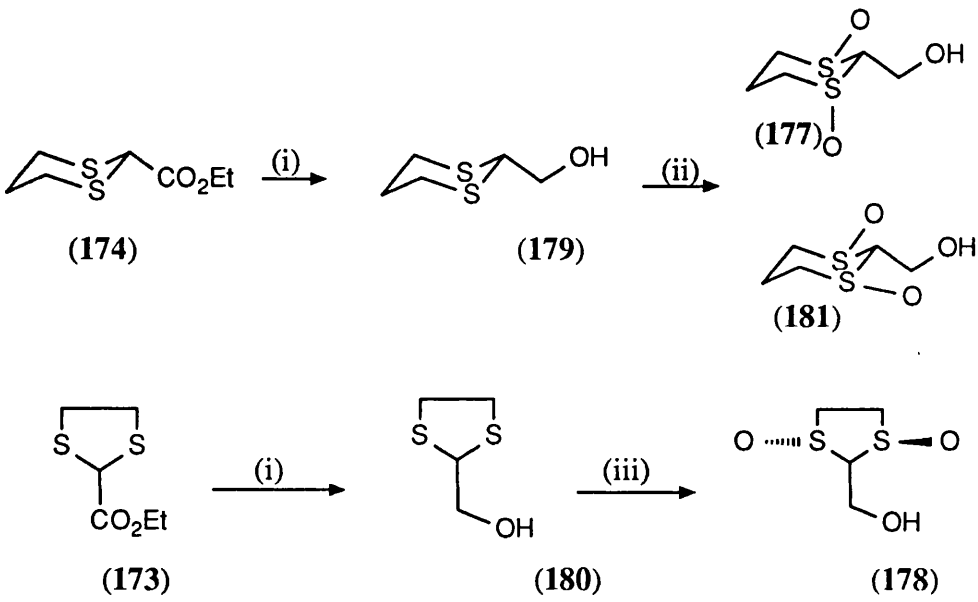
Scheme 2.24



(176)

Reduction of the bissulphide esters (**174**) and (**173**) was performed smoothly with LAH in THF at -78°C in 98% yield (**Scheme 2.25**). Subsequent oxidation to the dioxide alcohol was achieved in both cases with sodium periodate under normal conditions. In the oxidation of the dithiolane disulphide (**180**) the sole product of the second oxidation was *trans- bis* sulphoxide in 48% yield. In contrast, the second oxidation of the six membered dithiane (**179**) was found to be nonselective affording a 1:1 mixture of *cis* and *trans-bis* sulphoxides that could not be separated by chromatography.

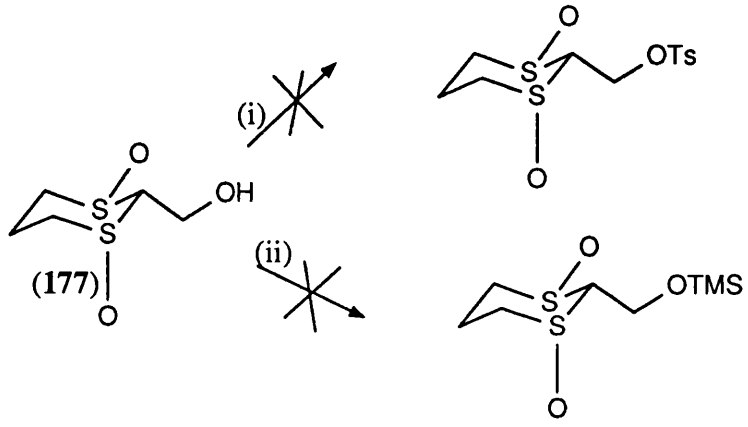
Scheme 2.25

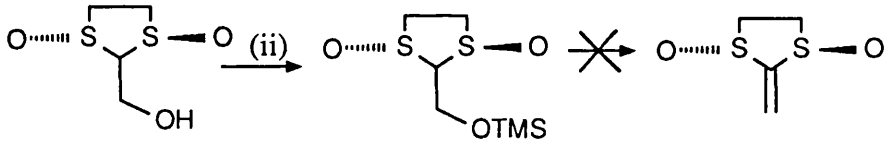


Reagents: (i) LAH, THF, 0°C, 1Hr; (ii) $NaIO_4$, MeOH, H_2O, 60°C, 2Hr.
(iii) $NaIO_4$, H_2O, MeOH, rt, 48Hr.

The synthesis of the desired dienophiles now only required elimination of the hydroxyl group. Attempts to form the tosylate under standard conditions failed and the reaction gave rise to a complex series of compounds when monitored by TLC (**Scheme 2.26**). Silylation of the hydroxyl group [142] was attempted under standard conditions for both ring sizes. In the dithiolane case the O-siloxy adduct (**183**) was obtained in 70% yield but attempts to repeat this reaction on the analagous six membered substrate all failed. DBU elimination of the dithiolane O-siloxy compound was found to afford baseline material indicating decomposition.

Scheme 2.26





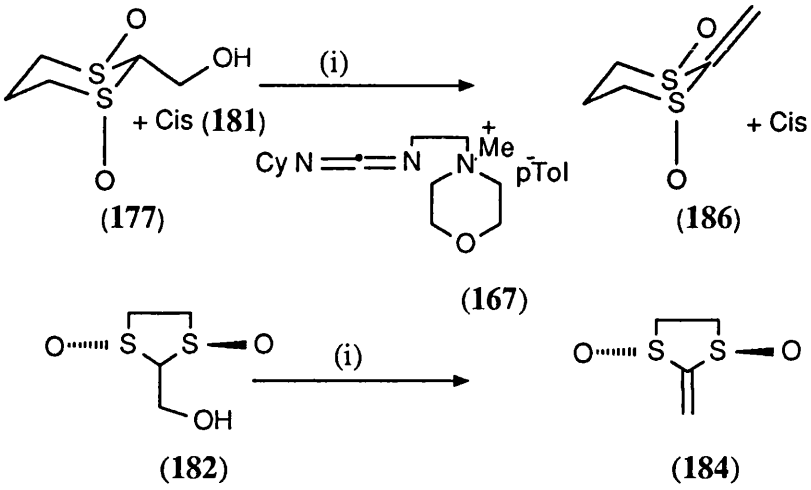
(178) **(183)** **(184)**

Reagents: (i) TsCl, py, rt; (ii) TMSCl, Py, HMDA

Dehydration with the water soluble DCC variant CMC MPT[127] (**167**, see page 70), used in the attempted dehydration of the benzodithiole hydroxymethyl *trans* dioxides (**158**), was found to be an effective dehydrating reagent for both alcohols (**177,178**). Dehydration was also successully effected using disuccinamydl carbonate (DSC) (**185**)[143].

CMC MPT was found to dehydrate the *cis* and *trans* mixture of dithiane alcohols (**177**) and (**181**) into a separable mixture of *cis* and *trans* dioxides from which (**186**) was isolated in 60% yield (**Scheme 2.27**). The *trans* dithiolane alcohol (**178**) was dehydrated under the same conditions affording the alkene (**184**) in 54% yield.

Scheme 2.27



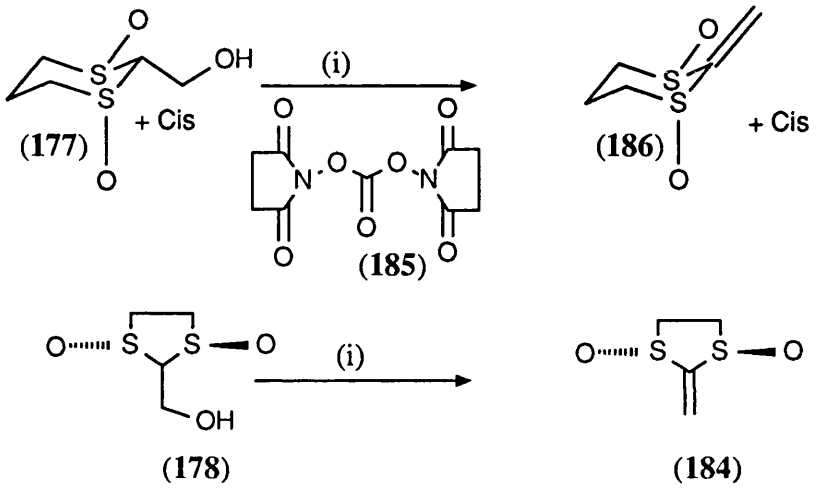
Reagents: (**167**)CH_3CN, $CuCl_2$ (cat), rt, 24Hr.

The urea formed as a by-product in this reaction was removed by passing the solution through a Florisil column and the copper (II) chloride (used catalytically) was also removed by the same purification. The urea may not be removed by aqueous wash due to the reactive nature of the alkene which reacts with water, reforming the alcohol. The addition of water to the alkenes appears to be more facile for the dithiolane (**184**) than for the 2-methylene-1,3-benzodithiole (**142**) indicating enhanced reactivity. In contrast the dithiane (**186**) appears to be relatively stable and is less reactive than the two five membered ring systems.

The second dehydrating reagent mentioned was also successful in dehydration of both the six and five membered ring alcohols. Disuccinamydl carbonate (**185**)[143] has been employed in the synthesis of methylene amino acids by dehydration.

Reaction with a mixture of (**177**) (**181**) and DSC/triethylamine gave a 54% yield of the readily separable *trans* alkene (**186**) (**Scheme 2.28**). However dehydration of the substituted dithiolane (**178**) led to (**184**) but only in 7% yield.

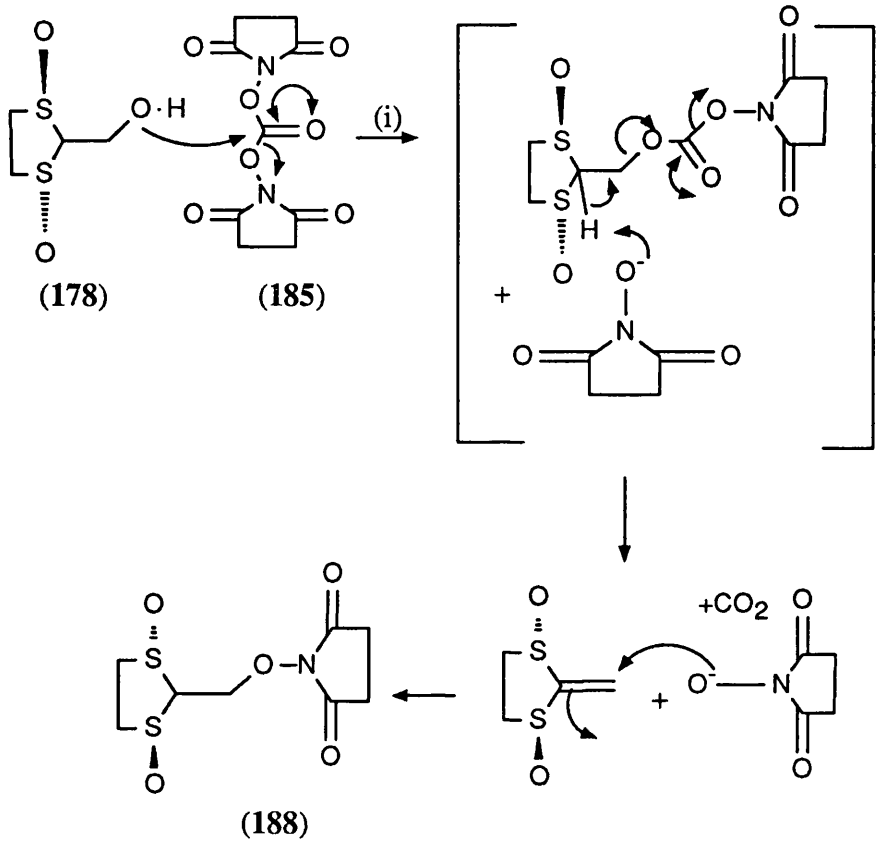
Scheme 2.28



Reagents: (i) CH_2Cl_2, (**186**), Et_3N, rt, 8hr.

The by product of this reaction the succinamidyl alcohol (**Scheme 2.28**) may possibly attack the more reactive dithiolane (**184**) upon concentration. Although not isolated, the succinamdyl ether (**188**) may account for the low yields observed.

Scheme 2.29



(178) (185) (188)

Reagents; (i) (**185**), Et_3N, acetone.

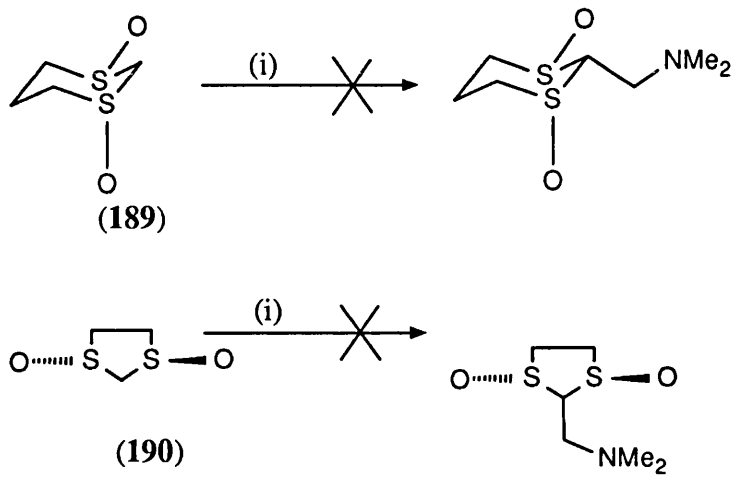
Although both dehydrating reagents are viable DSC was not employed due to the low yield of the dithiolane alkene (**184**).

2.6 Miscellaneous Reactions

Although access had been gained to the required dithiane (**186**) and dithiolane (**184**) exocyclic alkenes. Subsequent reactions were investigated to improve upon the yields of (**186**) and (**184**). Due to the success of the Mannich reaction on the 1,3-benzodithiole dioxide (**152**), identical Mannich conditions were applied to the unsubstituted *trans* dioxides of both the five and six membered *bis* sulphoxides (**189**)

and (**190**) (**Scheme 2.30**). Under these conditions none of the desired amine could be isolated. **Table 2.6** shows the various conditions subsequently investigated.

Scheme 2.30



Reagents; (i) HCL (conc), EtOH, $HNMe_2$, $(CH_2O)_n$
50°C.

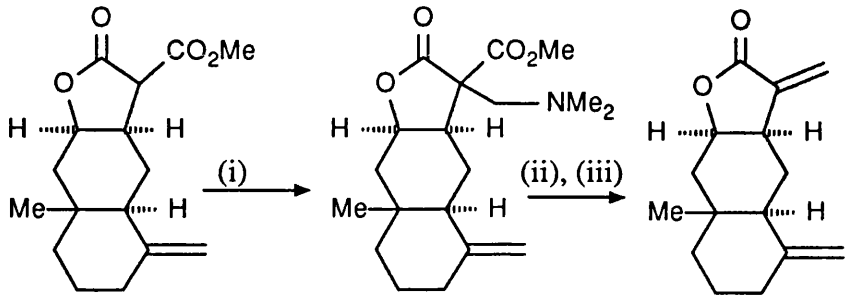
Table 2.6

Entry	Bis-sulphoxide	Conditions	Result
1	(**189**)	H_2O,HCl, HCHO, $HNMe_2$	No starting
		60°C, 24h	material, Baseline
2	(**190**)	H_2O,HCl,HCHO,$HNMe_2$	Starting material
		60°C, 24h	Baseline

The α-methylene of the γ-buryrolactone, isoalantolactone has been synthesised by a modified Mannich reaction by Miller et al[144] and Van-Tamelen[145]. Miller performed a Mannich reaction on the lactone ester (**191**) to give the amine (**192**) following salt formation with methyliodide. Refluxing in DMF effected ester hydrolysis and elimination (**Scheme 2.31**). In our hands under the same conditions, no

amine was isolated.

Scheme 2.31

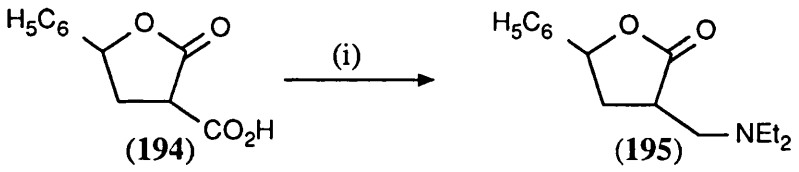


(191) **(192)** **(193)**

Reagents: (i) dioxane, $HNMe_2$, H_2NMe_2Cl, HCHO, 12Hr rt; (ii) MeI, CH_2Cl_2; (iii) DMF, 80°C, 12Hr.

Van-Tamelen applied an alternative approach applying Mannich conditions to the α-acid (**194**) (**Scheme 2.32**). The amine (**195**) was afforded by decarboxylation.

Scheme 2.32



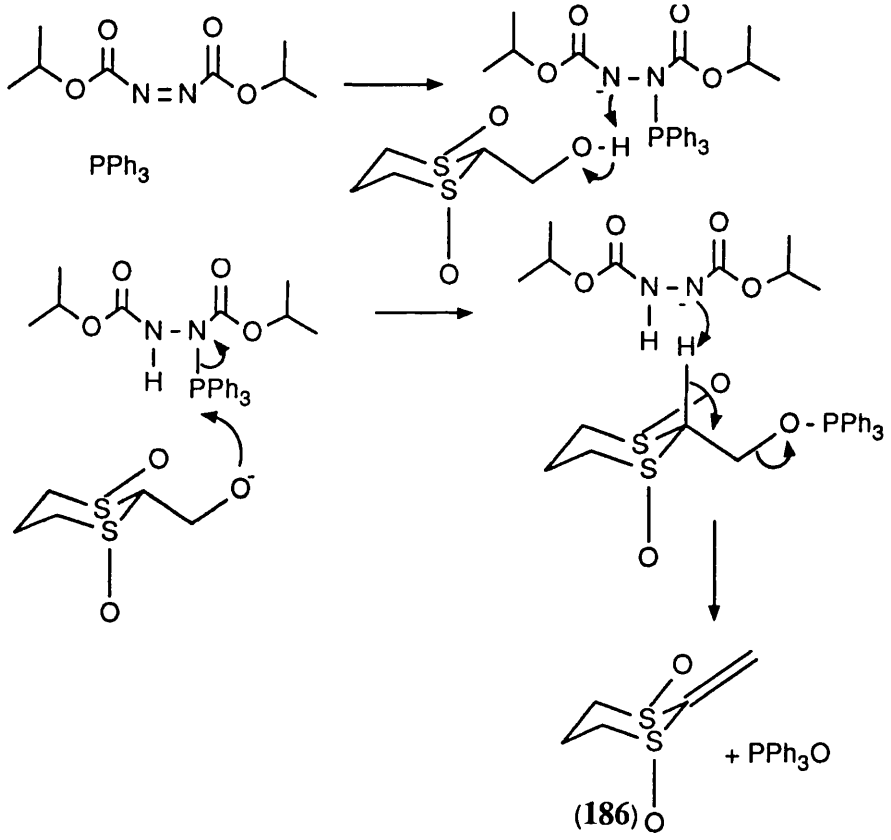
Reagents: (i) $(C_2H_5)_2NH$, $(CH_2O)_n$, EtOH

A Review of the literature on transformation of esters to acids indicated that this route was not viable due to expected competitive sulphoxide hydrolysis[146] with this information we were dissuaded from further investigation.

The Mitsunubo reaction[147] (**Scheme 2.32**) has been shown to result in

eliminated products (**186**) in the absence of acid. This reaction was attempted on substrate (**177**). During the course of the dehydration reaction triphenylphosphine oxide was produced but only in a small quantity.The starting material largely remained and no evidence of product was apparent.

Scheme 2.33



Anion chemistry of the dithiane *bis* sulphoxide (**189**) has been investigated by co-workers within the group[148]. With a non-racemic synthesis of (**186**) as a secondary goal, the feasibility of reacting formaldehyde[149] with the anion of (**189**) was investigated. Initial attempts involved formation of the anion with ^{n}BuLi, LDA or KHMDS followed by the addition of paraformaldehyde or gaseous formaldehyde. Under these conditions no reaction was observed. Due to the extensive work on the

dithiane anion the main cause for the failure of these reactions was attributed to the source of formaldehyde.

Two papers, N-L Yan et al[150] and Schlosser et al[151] promoted the use of monomeric formaldehyde as a THF solution as a superior synthetic reagent for hydroxymethylation. Indeed in our hands hydroxymethylation of the dithiane *bis* sulphoxide (**189**) proceeded smoothly to afford the *trans bis* hydroxymethyl adduct in 72%.

For the racemic series this route was not employed even though the yields were higher as the reduction of the ester followed by oxidation could be performed on larger scale without the necessity to generate the sensitive formaldehyde source before each reaction. However, for a non-racemic synthesis this route is attractive due to availability of enantiomerically pure dithiane dioxide (**189**).

2.7 Conclusion of successful synthesis of *bis* oxides of cyclic ketene thioacetals

The initial target of the α-methylene compounds (**142**), (**184**) and (**186**) had been achieved. For (**142**), anthranilic acid could be transformed into the tetrafluoroborate salt (**141**). Reduction and oxidation afforded the C-2 symmetric *trans* dioxide (**152**). Subsequent Mannich conditions in aqueous media gave amine (**172**) which could be eliminated to the alkene (**142**) in quantitative yield with methyl iodide.

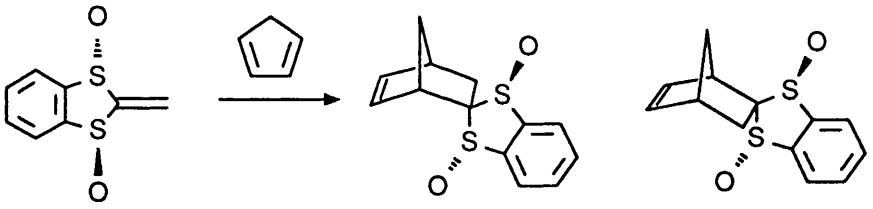
The dithiolane (**186**) and dithiane (**184**) methylene *bis* sulphoxides could not be synthesised *via* the Mannich reaction. Reduction of the commercially available disulphide esters (**173**) and (**174**) to the corresponding alcohols (**179** and **180**) followed

by oxidation gave the *trans bis* sulphoxides (**177,182**). Dehydration with CMC MPT (**185**) gave the two α-methylene compounds (**184**) and (**186**) in 50% yield.

2.8 Diels-Alder reactivity of (1RS,3RS)-2-methylene-1,3-benzodithiole-1,3-dioxide (142)

The Diels-Alder reactivity and selectivity of (**142**) was initially investigated with cyclopentadiene under a range of conditions. Under trial conditions, **scheme 2.34**, toluene at room temperature for twenty four hours the cycloadduct was obtained in 70% yield as a 2.5:1 ratio of (**196**):(**197**). The diastereomers were inseparable by chromatography. The assignment of the relative stereochemistry of the adducts is given later.

Scheme 2.34



(**142**) Major(**196**) Minor(**197**)

To optimise diastereoselectivity conditions such as solvent[152,153] and temperature[154] were varied. Other known effects such as the hydrophobic effect[155,156] (aqueous reactions), pressure effects[157], hydrogen bonding[158] and Lewis acid catalysis[159] were also investigated.

The effect of solvent on rates of Diels-Alder reactions is normally small. Enhancment of rate and selectivity with increasing dielectric constant for the solvent (polarity) is rarely seen above a factor of ten. The small rate increases are due to

stabilisation of the slightly polar transition state. Even though the Diels-Alder reaction is concerted it is evidently asychronous tending to a slight build up of charge in the transition state.

With dienophile (**142**) solvents with increasing dielectric constant showed an increase in rate and an increase in selectivity. **Table 2.7** shows the diastereomeric excess found for each solvent with the accompanying increase in rate.

Table 2.7 Diels-Alder reaction of dienophile (142) with cp; effect of slovent.

Entry	Solvent	Reaction Time (hr)	Dielectric constant	de
1	Toluene	24	2.8	33%
2	CH_2Cl_2	10	9.1	64%
3	Acetone	3	20.7	74%
4	DMSO	25	-	77%
5	CF_3CH_2OH	3	-	81%
6	H_2O	0.5	7.8	76%

Trifluoroethanol is known to be a very good hydrogen bonding acceptor[160] and should form such bonds with the sulphoxides of the dienophile. Reaction in aqueous media will be discussed in a later section, however in this context both polarity and hydrogen bonding may enhance the rate and selectivity.

Hydrogen bonding of solvent molecules to the sulphinyl oxygen would increase the effective size of the sulphoxide and this is thought to further disfavour the

approach of the diene in one direction.

High pressure has been used to accelerate Diels-Alder reactions by virtue of the reaction possessing an negative activation volume[157] . As the adducts posses a smaller volume than the starting material, pressure drives the reaction forward. **Table 2.8** shows the outcome of high pressure Diels-Alder reactions.

Table 2.8 Diels-Alder reaction of (142) with cp; effect of pressure.

Entry	Solution	Temperature	Time(hr)	Pressure	de
1	TOL	25°C	3 hr	5KBar	58%
2	TOL	25°C	3 hr	10KBar	64%
3	TOL	30°C	1.5 hr	•)))	50%

Entry 2 shows a slight increase in selectivity for the reaction at elevated pressure and both show an increase in rate over the reaction performed at atmospheric pressure.

The small effect on selectivity maybe attributed to both diastereomeric transition states having a similar negative activation volume. Large pressure effects would only be seen if one diastereomer has a smaller activation volume than the other. For Diels-Alder reactions in which endo and exo isomers occur, pressure will normally increase the proportion of endo isomer due to the smaller activation volume of the transition state.

Ultrasound[161] was found to increase the rate (entry 3, **table 2.8**) and the time required for the completion of the reaction reduced from 24 hr to 1.5 hr.

Ultrasound may be viewed as a combination of both temperature and pressure effects. Localized cavitation of solvent creates high localized temperature and pressure.

Investigations of the effects of Lewis acids on the rate of selectivity of the Diels-Alder reaction were also carried out and the results for the reaction between cyclopentadiene and the dienophile (**142**) are shown in table 2.9.

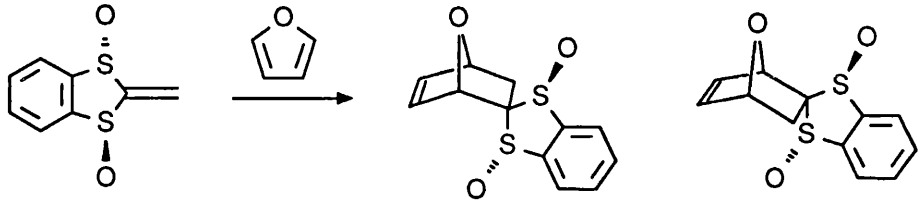
Table 2.9 Diels-Alder reaction between (142) and Cp; effect of Lewis acid.

Entry	Solvent	Reaction Time	Lewis Acid	Temperature	de
1	CH_2Cl_2	-	$TiCl_4$	-78°C	Dienophile destroyed
2	CH_2Cl_2	3 hr	$Ti(iPrO)_4$	-0°C	70%
3	CH_2Cl_2	3 hr	$AlCl_3$	-78°C	71%
4	CH_2Cl_2	1.5 hr	$SnCl_4$	-78°C	73%
5	THF	4 hr	$MgBr_2$	-78°C	79%
6	THF	4 hr	$ZnBr_2$	-78°C	71%
7	Et_2O	$1^1/_2$hr	$ZnCl_2$	-0°C	60%
9	CH_2Cl_2	0.25 hr	BF_3Et_2O	-78°C	86%

Mild Lewis acids, entries 2,5,6, and 7 showed moderate selectivity, but very strong Lewis acids decomposed the dienophile (entry 1). The best reactivity and selectivity was seen with $BF_3.Et_2O$ affording adducts in good overall yield, 74% from amine (**172**). The selectivity with other dienes such as furan, isoprene and 1-methoxybutadiene under the same reaction conditions were investigated. The less reactive diene furan (**scheme 2.35**) was found to be, as expected, less selective (**table**

2.10). Tin (IV) chloride provided the furan adducts (**200**) and (**201**) in excellent yield (98%),and moderate diastereoselectivity (7:1).

Scheme 2.35



(**142**) Major(**200**) Minor(**201**)

It was assumed that the relative stereochemistry of the major diastereomer of the furan reaction was the same as the cyclopentadiene adduct. **Table 2.10** shows the conditions investigated for reaction with furan.

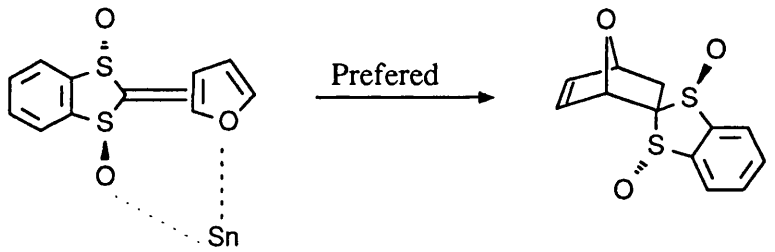
Table 2.10 Diels-Alder reaction of (142) with furan; effect of lewis acid.

Entry	Solvent	Lewis Acid	Time	Temperature	de
1	CH_2Cl_2	-	36 hr	Rt	3:1
2	CF_3CH_2OH	-	3 hr	Rt	4:1
3	CH_2Cl_2	ZnI_2	5	Rt	2:1
4	CH_2Cl_2	$ZnBr_2$	6 hr	Rt	1.8:1
5	CH_2Cl_2	BF_3Et_2O	1 hr	-78°C	3:1
6	CH_2Cl_2	$SnCl_4$	1 hr	-78	7:1

The normal cause of poor selectivity in Diels-Alder reactions with furan is due to reversibility[165] and the reaction being under thermodynamic rather than kinetic control. However after subjecting the 2:1 ratio of furan cycloadducts to $SnCl_4$ at -78°C

in CH_2Cl_2, no change in this ratio was observed. Thus, furan reactions with $SnCl_4$ are under kinetic control: no equilibration was occurring. The increase in selectivity (entry 6) may be attributed to the oxophilic nature of tin (IV) chloride allowing coordination between both the vinyl sulphoxide and the oxygen of furan. Simultaneous coordination of these two oxygens by Sn would give the same major diastereomer as formed in reactions with cyclopentadiene (**scheme 2.36**).

Scheme 2.36



(200)

The promising reaction in water, 30 min 74% de, prompted exploration of another effect associated with Diels-Alder reactions namely the hydrophobic effect. The hydrophobic effect has been investigated by Breslow[162] and Grieco[163], and is defined as the "tendency of nonpolar species to aggregate in water solution so as to decrease the hydrocarbon - water interfacial area". This statement assumes that water molecules have a preference for interaction with other water molecules rather than interaction with a hydrocarbon surface. This hydrophobic effect is thought to be important in protein folding, determining the tertiary protein structure of enzymes.

The hydrophobic effect may be enhanced or diminished by the addition of 'salting in' or 'salting out' reagents[164]. **Table 2.11** shows the result of Diels-Alder reactions performed under aqueous conditions.

Table 2.11 Diels-Alder reaction of (142) with Cp; investigation of the hydrophobic effect.

Entry	Added salt	Time (min)	de
1	None	30	75%[a]
2	1M $LiClCO_4$	30	71%
3	2.5M $LiClCO_4$	30	82%
4	2.5M LiCl	30	72%
5	5.M LiCl	30	81%
6	5.M NaCl	30	78%

a under these conditions competative addition of water occurred. The hydroxymethyl adduct was obtained in 20% yield together with 80% yield of the Diels-Alder adduct.

Entry 1 shows the enhanced reactivity and selectivity in aqueous solvent compared to that of toluene 33% de, 24 hr. This enhanced selectivity may be attributed to hydrogen bonding of water molecules to the sulphinyl groups and or hydrophobic effects. In practise the hydrophobic effect operates by aggregation of non polar hydrocarbon regions of the reactants effectively applying an internal pressure to the diene and dienophile. Aggregation of non-polar hydrocarbons minimises the unfavorable water-hydrocarbon interactions. An increase in the rate of Diels-Alder reactions in water can be attributed to the fact that the transition state has less water-hydrocarbon interactions compared to the starting materials. Any factor that stabilises the transition state over starting material will result in an increase in rate.

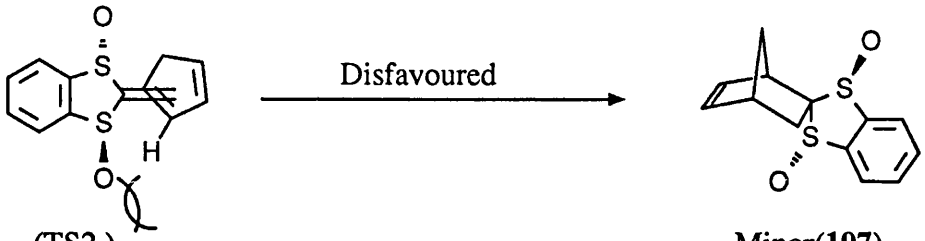
The enhanced selectivity with the addition of certain salts is attributed to an enhanced hydrophobic effect where the salt is a 'salting out' reagent[164]. This salt favours water-water interactions and disfavours water-hydrocarbon interactions further.

'Salting in' reagents reduce the strength of water-water interactions thus favouring water-hydrocarbon interactions. 'Salting in' salts should reduce the hydrophobic effect and thus reduce the rate. The salts LiCl and NaCl are 'salting out' reagents and $LiClO_4$ is a 'salting in' reagent. In our hands addition of salting in or salting out reagents did not result in a significant difference in rate and selectivity relative to water alone.

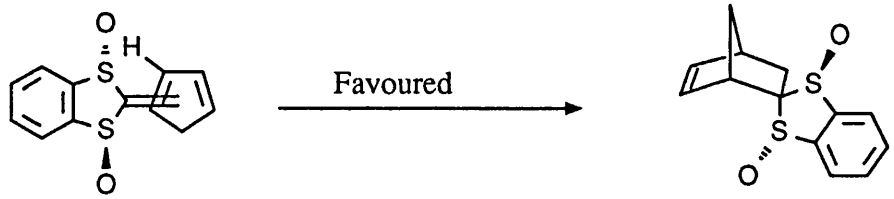
It was noticed that the Diels-Alder reaction in water alone (entry 2) occurred with competitive addition of water to the alkene affording the hydroxymethyl *bis* sulphoxide (**164**) in 20% yield. In the reactions involving salt no addition was seen indicating that the cycloaddition was faster than addition of water. Thus either the rate of Diels-Alder reaction had increased or the rate of addition of water had decreased or possibly both.

Crystalisation of a 15:1 mixture allowed analysis by x-ray crystalography. From this the stereochemistry of the major cycloadduct was shown to be (**196**), see appendix one. The two possible transition states leading to (**196**) and (**197**) are shown in **scheme 2.37**. Since (**196**) is the major diastereomer TS1 is evidently favoured over TS2. This seems reasonable as TS2 suffers from the sulphinyl oxygen. Such interactions are not present in TS2 .

Scheme 2.37



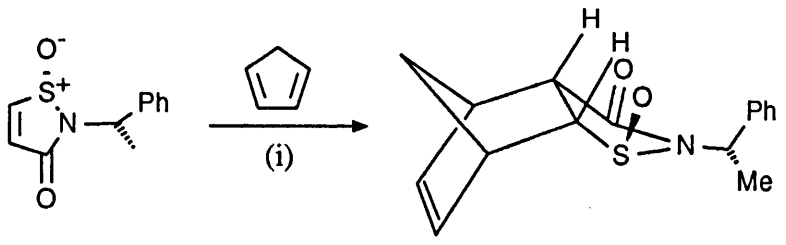
(TS2) Minor(**197**)



(TS1) Major (**196**)

Recrystallization of a 15:1 ratio of diastereomeric adducts afforded pure **(196)** the stereochemistry of which was determined by X-ray crystallography (appendix 1). Waldner[165] has similary observed that dienes prefer to approach the sulphinyl substituted dienophile on the same face as the lone pair rather than the face bearing the sulphinyl oxygen, (**Scheme 2.38**).

Scheme 2.38

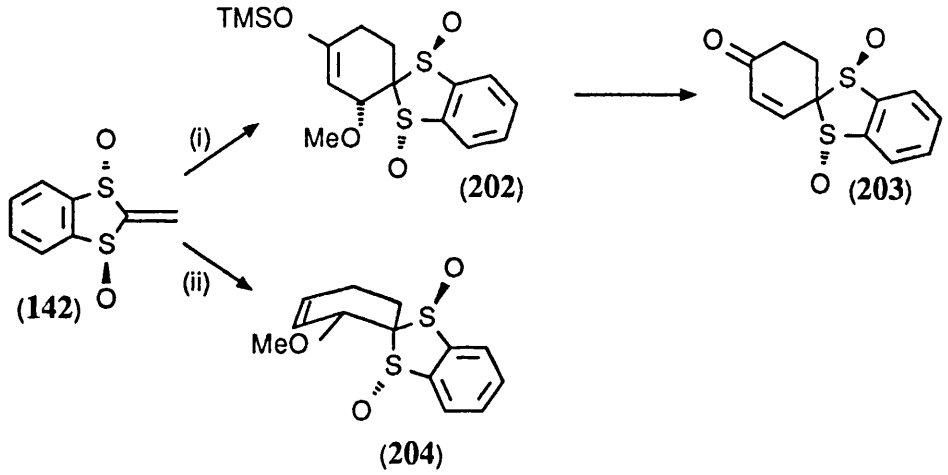


(198) **(199)** 95% de

Reagents: (i) 15min, 20°C.

The influence of the sulphoxide in directing the steric course of Diels-Alder reactions is further exemplified by the reactions of acyclic dienes such as Danifshefskys diene and 1-methoxybutadiene. Danishefsky's diene provided the siloxy adduct (**202**), **scheme 2.39** which was isolated as the enone (**203**) after work up. Reaction of 1-methoxybutadiene gave a single isomer (**204**) in 77% yield without catalysis (see appendix 1). In both case a single diastereomer was formed and was assumed to have the stereochemistry shown.

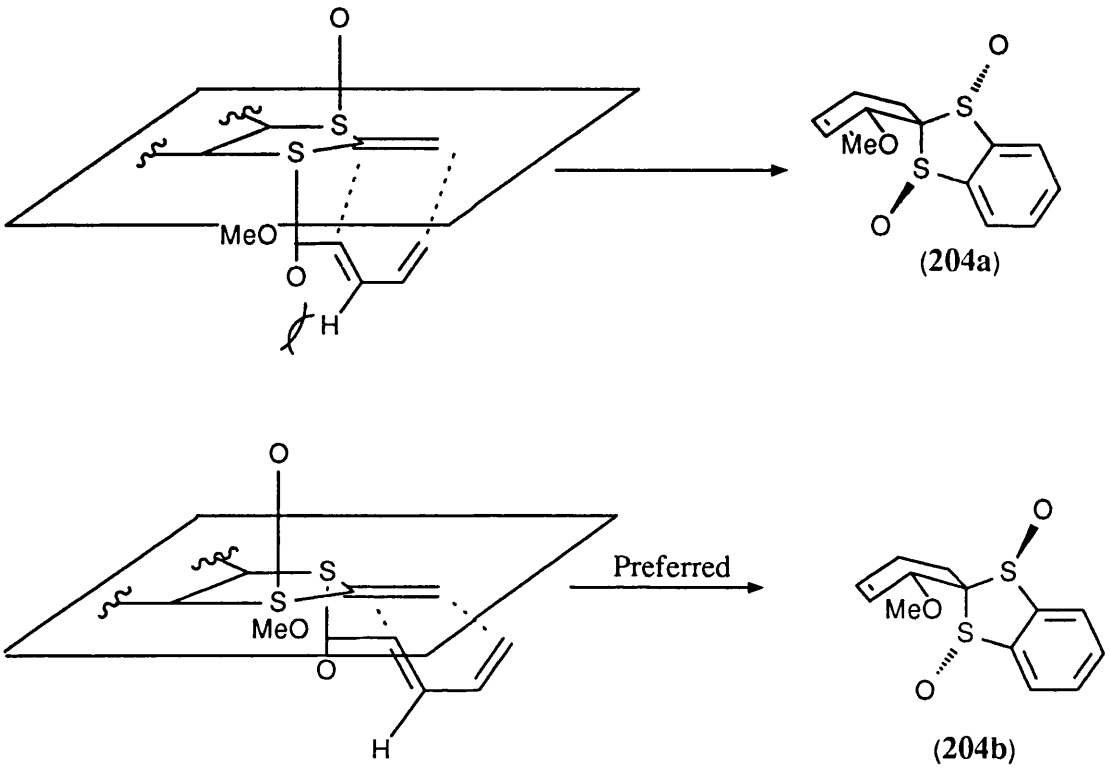
Scheme 2.39



Reagents: (i) $CH_2CH(OTMS)CHCHOMe, CH_2Cl_2$, 24hr;
(ii) 1-Methoxybutadiene, CH_2Cl_2, 24hr.

The excellent selectivity in these reactions is attributed to preferential approach of the methoxy diene over the sulphinyl lone pair rather than the sulphinyl oxygen. Production of the alternative diastereomer is disfavoured due to unfavourable sulphoxide/C-2 hydrogen interactions (**scheme 2.40**).

Scheme 2.40



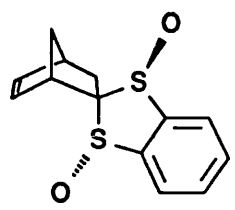
2.9 Comparison of five and six membered bis sulphoxide ketene equivalents.

Using the conditions that maximised the diastereoselectivity for Diels-Alder reactions between benzodithiole based dienophiles and various dienes, it was decided to investigate the Diels-Alder reactivity of dithiane and dithiolane based dienophiles.

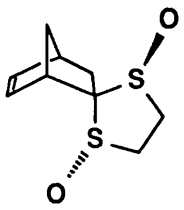
2.9.1 Diels-Alder reaction with various dienes.

Diels-Alder reaction of the five and six membered rings were performed under conditions shown in **table 2.12** The major diastereomer (**Scheme 2.41**) is assigned by analogy to the major adduct of reaction with 2-methylene-1,3 -benzodithiole (**Scheme 2.34**).

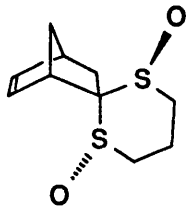
Scheme 2.41



(196)



(205)



(206)

Table 2.12 Diels-Alder reactions with Cp.

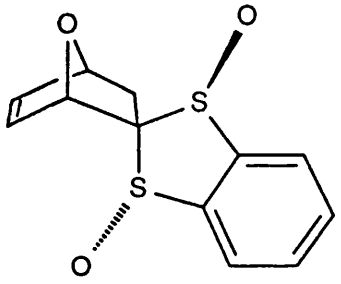
Entry	Dienophile	Conditions	Ratio	product	de
1	(**142**)	CH_2Cl_2/RT/10 hr	4.3:1	196	64%
2	(**184**)	CH_2Cl_2/Rt/10 hr	5.5:1	205	69%
3	(**186**)	CH_2Cl_2/Rt/36 hr	-	-	-
4	(**142**)	CH_2Cl_2/-78/ BF_3Et_2O/15 min	14:1	196	86%
5	(**184**)	CH_2Cl_2/-78/ BF_3Et_2O/15 min	25:1	205	92%
6	(**186**)	CH_2Cl_2/-78/ BF_3Et_2O/60 min	25:1	206	92%

Table 2.12 shows that under borontrifluoroetherate catalysis excellent diastereoselectivity was obtained. The comparative reactivity of the five membered ring over the six membered ring was noted entries (3) and (6). The increase in reactivity and selectivity of the dienophile (**184**) over (**186**) was attributed to extra ring strain in the five membered ring compared to the six membered ring.

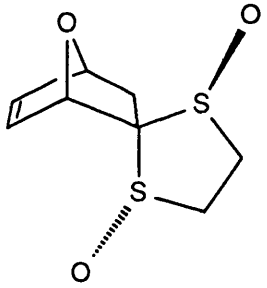
Reactions with furan were also investigated and the results shown in **table 2.13**.

Table 2.13 Diels-Alder reactions with furan.

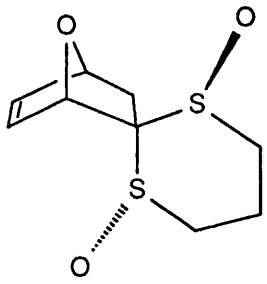
Entry	Dienophile	Conditions	product	de
(1)	(**142**)	CH_2Cl_2/Rt/36 hr	200	50%
(2)	(**184**)	CH_2Cl_2/Rt/24 hr	207	58%
(3)	(**186**)	CH_2Cl_2/Rt/36 hr	-	-
(4)	(**186**)	$CH_2Cl_2/BF_3Et_2O/-78^0C$	208	0%
(5)	(**142**)	$CH_2Cl_2/-78^0C/SnCl_4$/ 60 min	200	75%
(6)	(**184**)	$CH_2Cl_2/-78^0C/SnCl_4$/ 60 min	207	66%
(7)	(**186**)	$CH_2Cl_2/-78^0C/SnCl_4$/60 min		-



(**200**)



(**207**)

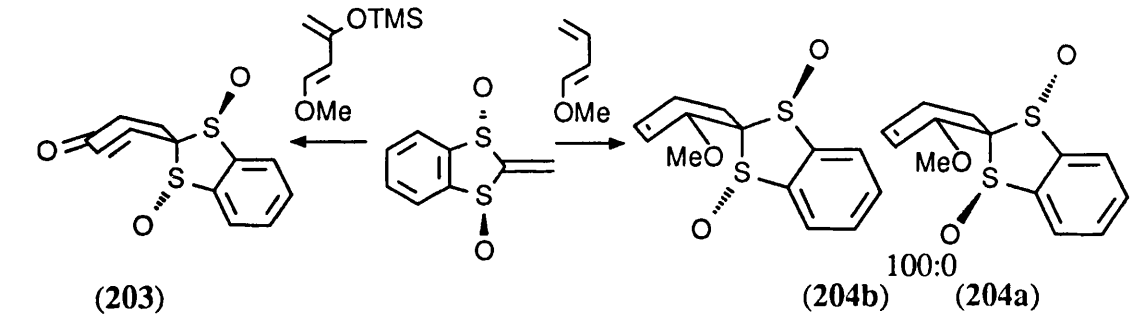


(**208**)

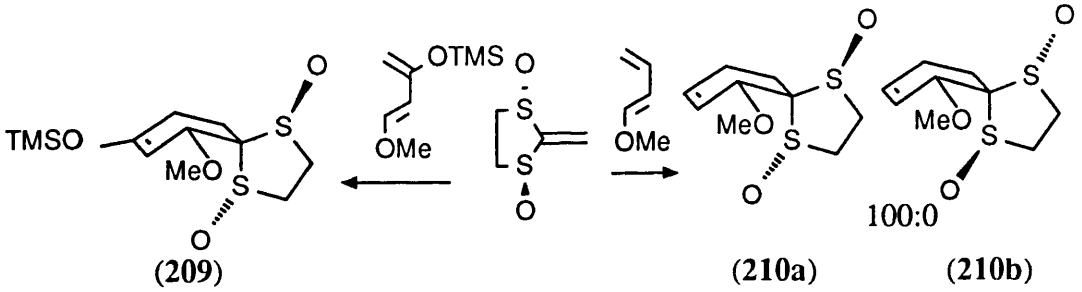
Tin (IV) chloride enhanced the rate and selectivity over the uncatalysed reaction (entries 5-7) and showed higher selectivity than boron trifluoroetherate catalysed reactions.

Reaction of (**184**) with acyclic dienes occured smoothly at room temperature to give a single diastereomer. Under the same reactions conditions no cycloadducts were obtained with the six membered ring dienophile (**186**). This lack of reactivity of the dithiane based dienophile with acyclic dienes maybe due to unfavourable steric interactions between the axial groups on the six membered ring. Neither of the two five membered ring dienophiles (**142**) or (**184**) groups in the same axial orientation which would interact with a 1-substituent on the diene.

Scheme 2.41



(203) (204b) (204a)



(209) (210a) (210b)

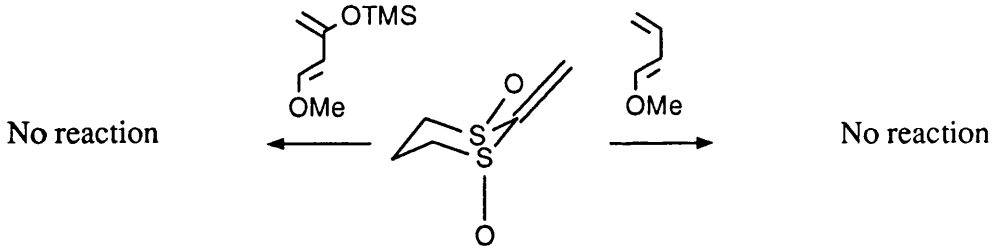
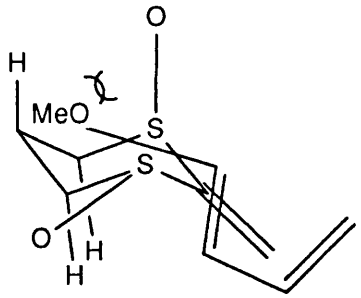


Fig. 2.4

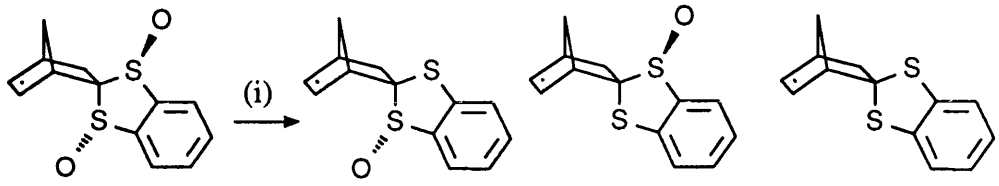


2.9 Synthesis of bicyclo[2.2.1]hept-5-ene-2-one; Hydrolysis of cyclic bis sulphoxides

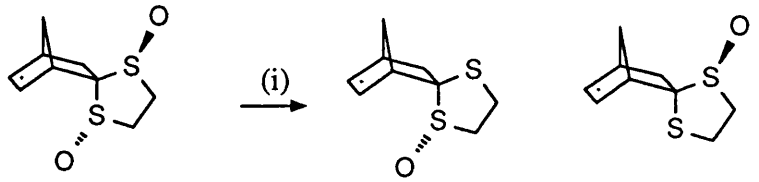
To realise the potential of our dienophiles to act as ketene equivalents, the cyclic *bis* sulphoxide must be transformed into a ketone. Much literature has been produced on the transformation of dithiane and dithiolane groups to a ketone. In contrast there are only a few examples of the direct hydrolysis of cyclic bis sulphoxides to carbonyl groups. Dithiane groups are often used as protecting groups for steroids. In one example the dithiane was oxidised to the *bis* sulphoxide and hydrolysed directly to the carbonyl by refluxing in 5% methanolic KOH[166]. However applying these conditions to compound (**205**) resulted in decomposition

An alternative method for the hydrolysis of a *bis* sulphoxide involved treatment with titanium (III) chloride in acetic acid.[97] Application of these conditions to compounds (**196**) and (**205**) was only partially successful (**Scheme 2.42**). In both the dithiolane (**205**) and 1,3 benzodithiole (**196**) Diels-Alder adducts, treatment with titanium (III) chloride gave the monoreduced compound (**210a,210b**) but no subsequent hydrolysis to the required ketone occurred.

Scheme 2.42



(196) **(211a)** **(211b)** **(213)**

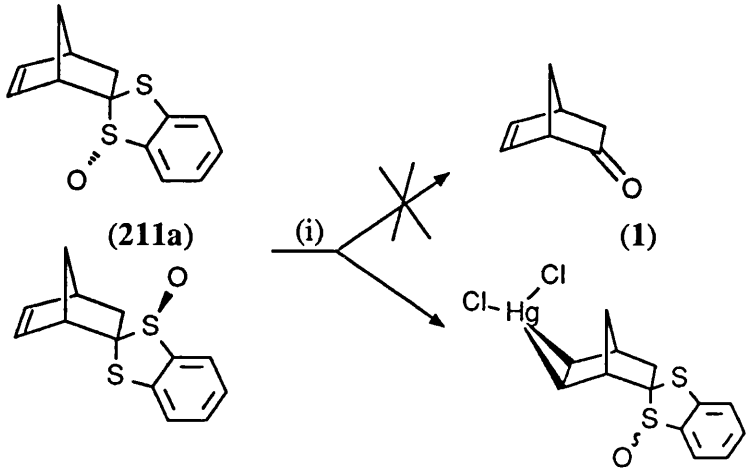


(205) **(212a)** **(212b)**

Reagents: (i) $TiCl_3$, AcOH, 15 min.

Previously hydrolysis of dithiane and dithiolanes has been achieved with mercuric chloride.[168] In our hands treatment of monoxides (**210a**, **210b**) or the bissulphide (**213**) with $HgCl_2$ (**Scheme 2.43**) gave none of the required ketone.

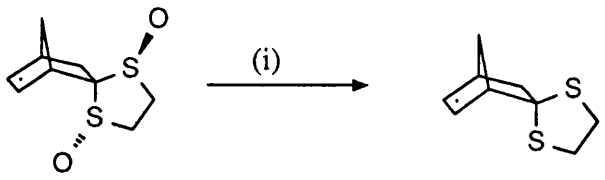
Scheme 2.43



Reagents: (i) $HgCl_2$, THF/HCl

Reduction of both sulphoxides appeared more attractive than mono reduction due to ease of isolation of the disulphide. Many methods of sulphoxide reduction have been published[168], but fortunately the first method investigated gave the bissulphide in excellent yield (**Scheme 2.44**), with simple purification. Phosphorous tribromide[167] at 0°C in methylene chloride gave bissulphide (**214**) in 98% yield.

Scheme 2.44

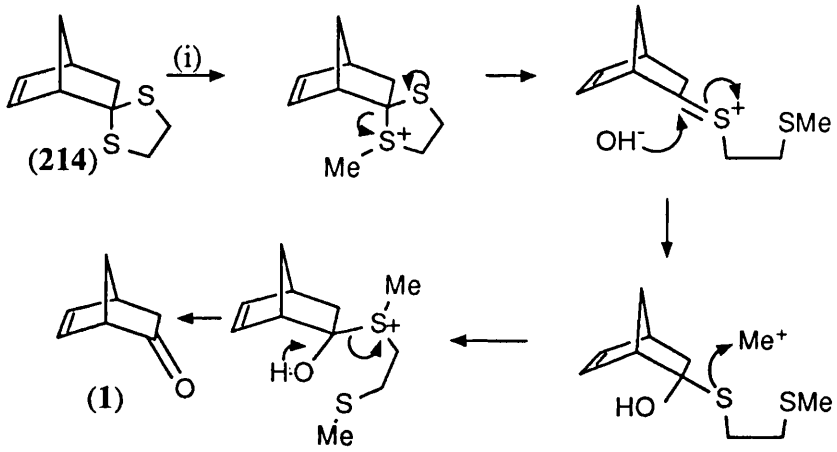


(**205**) (**214**)

Reagents: (i) PBr_3, CH_2Cl_2, 0°C.

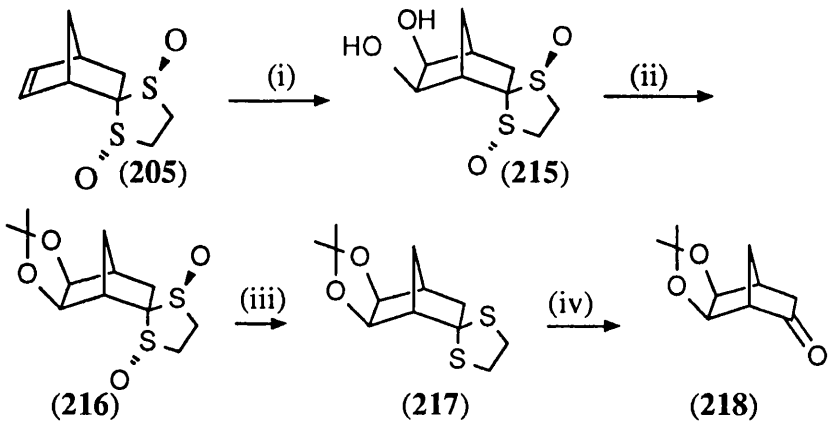
Subsequent reflux of bnissulphide (**214**) in acetonitrile with methyl iodide (**Scheme 2.45**) gave the required ketone (**1**)in 45% yield. The low yield was thought to be due to the volatility of the norbornenone[97](**1**). However reduction of the less volatile isopropylidine adduct (**216**) followed by hydrolysis (**Scheme 2.45**) gave the isopropylidine ketone (**218**) in good yield (65%).

Scheme 2.45



Reagents: (i)MeI, CH_3CN, Δ

Scheme 2.46



Reagents: (i) OsO_4, $(CH_3)_2CO$, H_2O, NMO; (ii) $(CH_3)_2C(OMe)_2$, pTSA $(CH_3)_2CO$; (iii) PBr_3, CH_2Cl_2, 0°C; (iv) MeI, CH_3CN, Δ.

The hydrolysis of the other two dienophiles would be expected to follow the same route.

2.12 Summary

The synthesis of three C-2 symmetric dienophiles from readily available anthranilic acid (dienophile (**142**)), ethyl-1,3-dithiolane-2-carboxylate (dienophile (**184**)) and ethyl-1,3-dithiane-2-carboxylate (dienophile (**186**)) has been achieved.

The Diels-Alder reactions of the three dienophiles has been optimized for cyclopentadiene, furan, 1-methoxybutadiene and Danifshefsky's diene.

Comparison of reactivity between the three dienophiles showed that the five membered rings were more reactive than the six. X-ray studies of the major diastereomer showed that the proposed mode of cycloaddition involved approach of diene over the sulphur lone pair rather than the sulphoxide. It was observed that the selectivity of the cycloaddition process was influenced by the addition of a reagent that

complexes to the sulphinyl oxygen. These results are in keeping with the proposed model for the mode of addition of the diene.

Hydrolysis of the cycloadducts was achieved to give the key synthetic intermediate norbornen-2-one (**1**).

CHAPTER THREE

CARBOCYCLIC NUCLEOSIDES

INTRODUCTION

CHAPTER 3

3.1 INTRODUCTION

In Chapter one some examples of the applicability of ketene equivalents to the synthesis of bicyclic ketones and their role as key intermediates in natural product synthesis were discussed. A range of mimetics of natural antibiotics and antiviral agents have been reported using ketene equivalents.[130] This area has received great interest over the past few years with the global epidemic spread of human immunodeficiency virus (HIV), the syndrome known as AIDS.[171] Having found a new ketene equivalent that reacted with high diastereoselectivity, it was decided to apply this chemistry to the synthesis of a carbocyclic nucleoside.

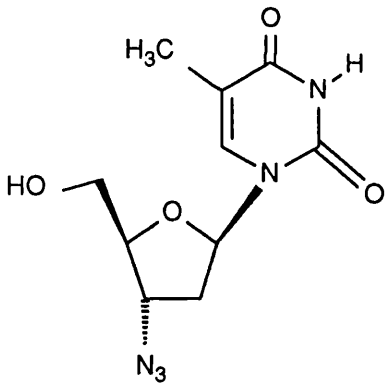
3.2 Carbocyclic Nucleosides as anti viral agents

Once a virus infects a cell it deposits viral enzymes and RNA. These enzymes convert viral RNA to DNA, cut host DNA and recombine incorporating viral DNA into host DNA. The incorporation of viral single stranded RNA into host double stranded DNA will cause chromosomal aberrations and allow the production of aberrant viral proteins *via* a chromosomal frame shift effect. It is the action of these abnormal proteins produced from infected cells that give rise to viral symptoms. To inhibit the virus,the enzyme reverse transcriptase may be blocked thus preventing the infection process: transcription of viral RNA into DNA.[172]

Systemic treatment of human viral infections has been slow due to the resistance to chemotherapy shown by such infections. The main problem in systemic treatment has been the intimate relationship between viral and host metabolism, making it difficult to destroy a virus without irreparable damage to the host cell.

Synthetic attempts to produce antiviral agents have successfully involved the application of carbocyclic nucleosides where the furanose ring has been replaced by a cyclopentane ring.[173] Carbocyclic analogs have been shown to be stable mimetics of the furanose metabolites.[174]

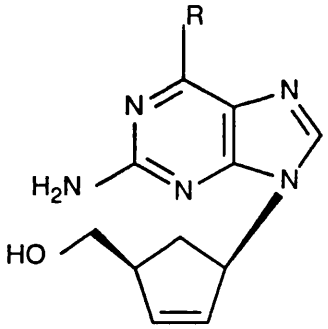
To date one of the most important viral infections, HIV, has had only a few therapeutic agents that show any affect at an acceptable dose levels the best known of these to survive clinical trials is azidothymidine (AZT) (**227**).[175] However AZT is associated with many side-effects including myelosuppression. Other anti HIV products products are currently being investigated including cytidine and purine analogs of the basic carbocyclic nucleoside.

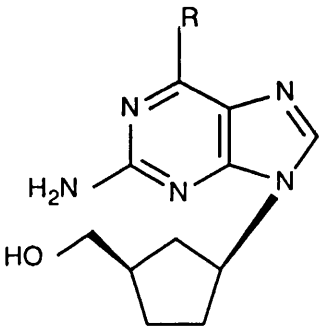


(**227**)

3.3 Carbocyclic 2′,3′, didehydro 2′,3′ dideoxy-2,6-disubstituted purine nucleosides as anti HIV agents.

In vitro studies show that the carbocyclic disubstituted purine nucleosides are potent inhibitors of the HIV virus.[176] A range of analogs have been produced and their ability to inhibit the effects of HIV induced cytopathogenicity in MT-2 cells investigated. **Table 3.1** shows the activity relative to a standard 2′,3′ dideoxycytidine, (DDC) which was previously the most potent of HIV replication inhibitors. Inhibition was defined as 50% reduction in cytopathic effect. The 2′,3′ unsubstituted guanosine derivative (Carbovir (**224a**)) was the most selective anti HIV compound.





(223a) R= Cl
(224a) R= OH
(225a) R= NH_2

(223b) R= Cl
(225b) R= OH
(225b) R=NH_2

Table 3.1: Activity of some HIV replicase inhibitors

Compound	EC_{50} mg/ml	IC_{50} mg/ml	TI
223a	0.40	6.97	17.3
223b	>100	>100	
224a	0.19	41.8	2.20
224b	>100	>100	
225a	4.7	>125.0	26.6
225b	16.7	>100	>5.9
DDC	0.29	44	152

EC_{50} : The effective concentration 50% EC_{50} indicates the concentration of test agent that increases formezan production in infected cells to 50% of untreated, uninfected cells.

IC_{50}: The inhibitory conc^n (IC_{50}) represents the 50% of the toxic Conc^n of drug that reduced Formezan production in uninfected cells to 50% of untreated cells.

TI: The theraputic index Ti is determined by dividing IC_{50} by EC_{50}.

Table 3.1 shows that (**224a**)[176] is the most potent inhibitor of the HIV virus. The chloro derivative (**233a**) was only less active by a factor of two, however its therapeutic index was found to be thirteen times lower.

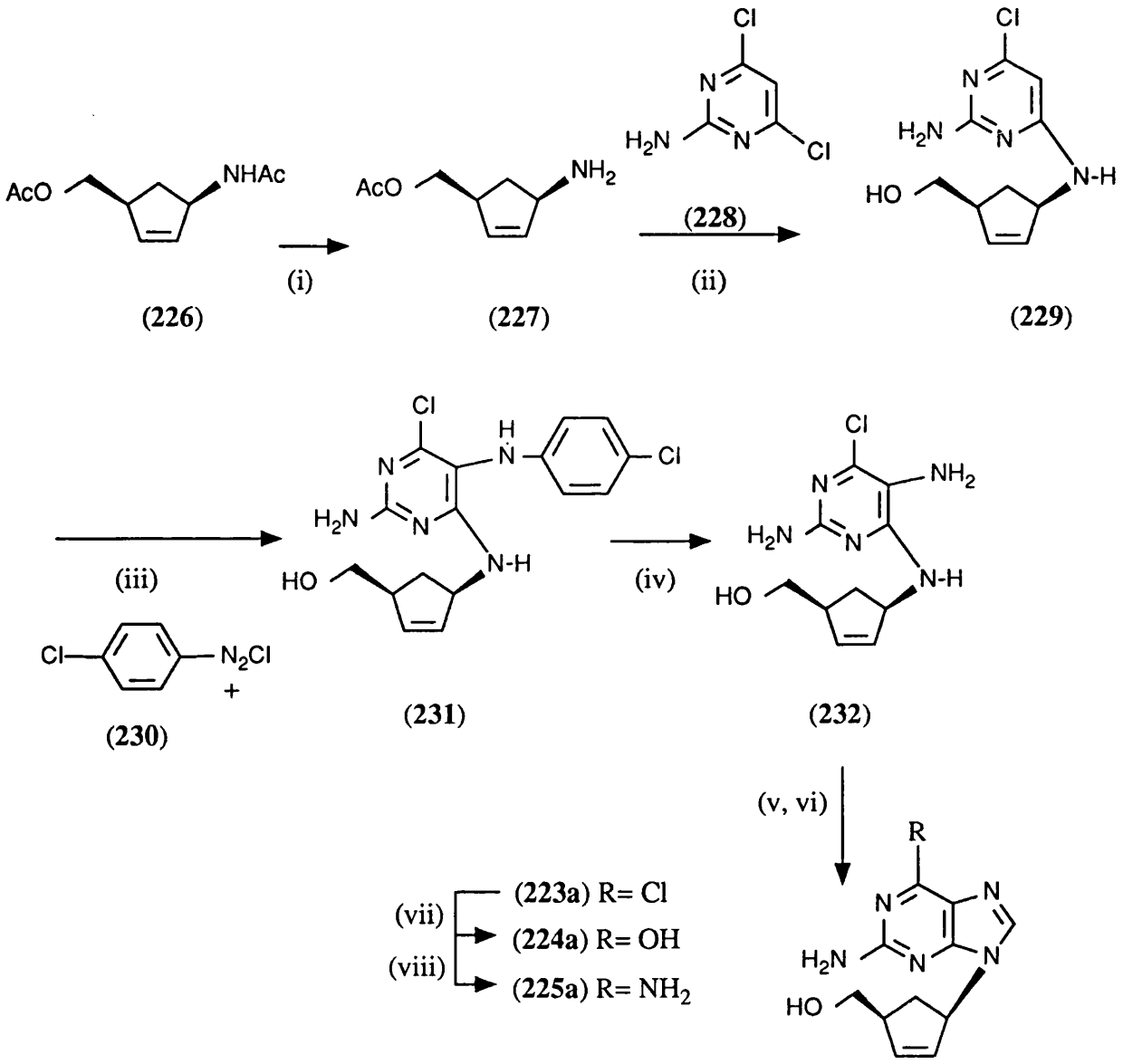
Carbovir (**224a**) represents one of the most promising selective anti HIV agents. It is stable to hydrolysis and has the ability to inhibit infection and replication at concentrations 200 fold (MT-2 cells) and 400 fold (CEM cells) below toxic concentration which makes it an excellent candidate for treatment of AIDS

patients.

3.4 Synthetic approaches to Carbovir

Carbovir and its analogs were first synthesised by Vince et al[176] by the route outlined in **scheme 3.1**. The N-acetoxy cyclopentene (**226**) was hydrolysed with barium hydroxide and condensed with 2-amino-4,6 dichloro pyrimidine to give (**229**). Subsequent reaction with p-chlorobenzendiazonium chloride followed by reduction with zinc and acetic acid gave pyrimidine (**232**). Ring closures by triethylformate and hydrolysis with 0.3N NaOH gave Carbovir (**224a**). The same synthetic route allowed synthesis of the saturated Carbovir analog from N-Acteoxy cyclopentane (**233**).

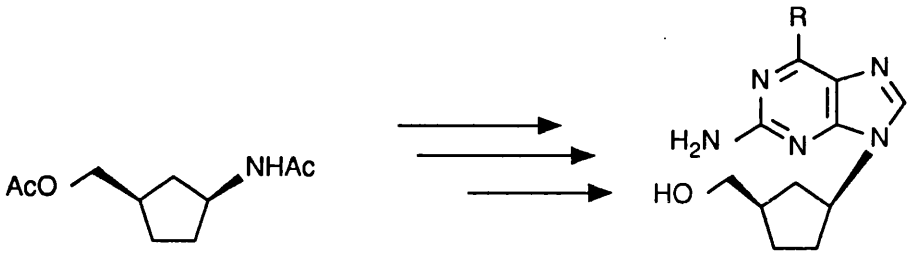
Scheme 3.1



Reagents: (i) BaOH, (ii) (**228**), NEt_3, BuOH, Δ, (iii) (**230**), AcOH, H_2O, $NaOAc{\cdot}3H_2O$

(iv) Zn, AcOH, H_2O, EtOH, Δ, (v) $(EtO)_3CH$, HCl, 12 N, (vi) HCl 0.5 N, pH 8, NaOH 1N

(vii) NaOH 0.33 N, (viii) NH_3, MeOH.

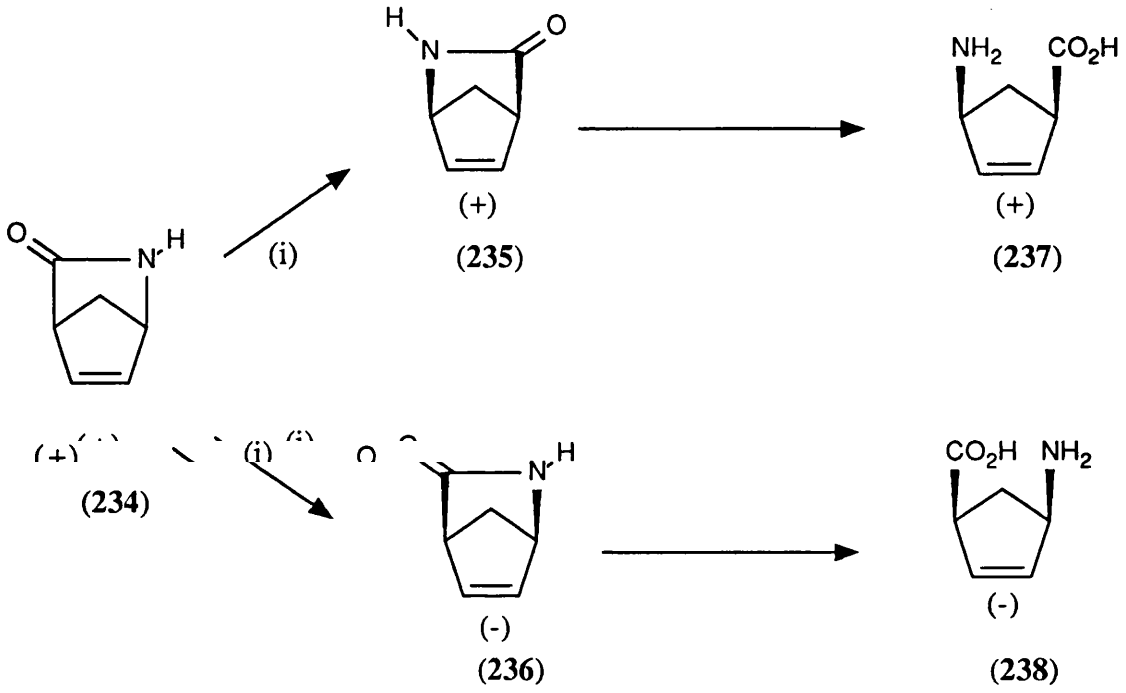


(**233**)

(**223b**) R= Cl
(**224b**) R= OH
(**225b**) R= NH_2

Enantiomerically pure Carbovir has been synthesised by two methods. The first involves modification of the natural produced aristeromycin but as aristeromycin is not readily available, this route is limited. The second involves enzymatic resolution of (±)2-azabicyclo [2.2.1]hept-5-ene-one (**234**)[177] (**scheme 3.2**). This intermediate is generated from addition of tosylcyanide to cyclopentadiene followed by acid work up. Hydrolysis of lactams (**235**) and (**236**) gave amino acids (**237**) and (**238**) which were separated, both of which were afforded in greater than 98% ee.

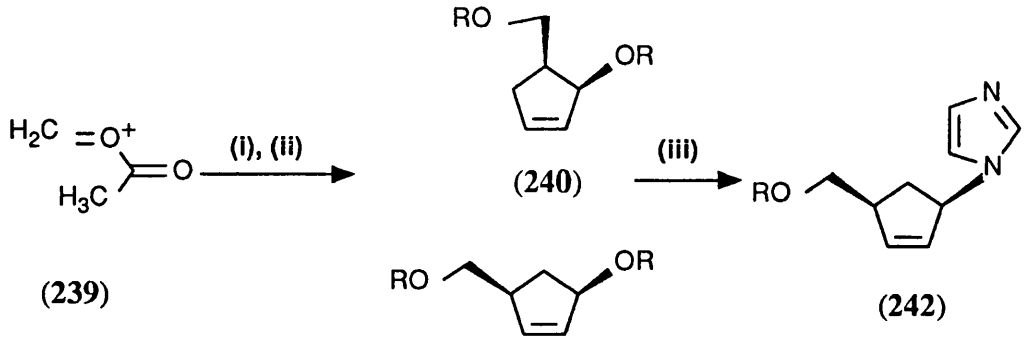
Scheme 3.2



Reagent: (i) Pseudomonas Microorganisim

(-) lactam (**236**) was converted into (-) Carbovir[177] (**223a**) by the route shown in **Scheme 3.2.** Analogues of carbovir have been prepared by the route shown in **scheme 3.3**

Scheme 3.3

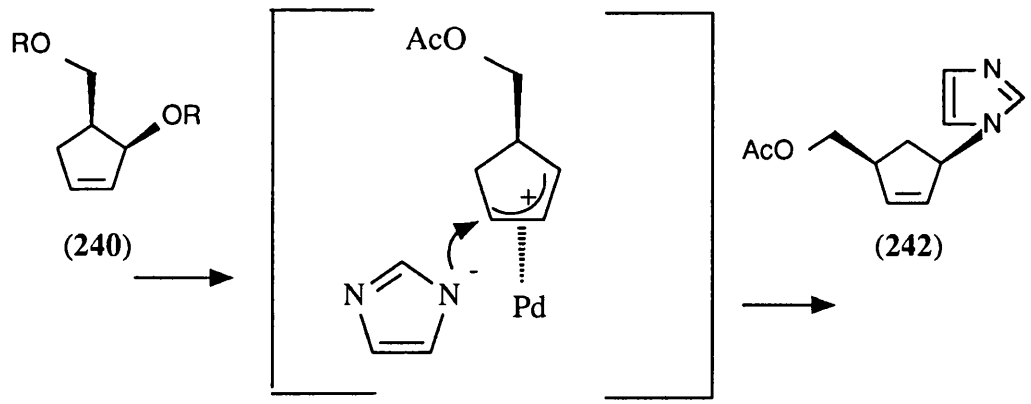


R= OAc

Reagents: (i) C_5H_5, (ii) Ac_2O, (iii) $C_3H_3N_2$, Et_3N, THF, $Pd(Ph_3)_4$, 50^0C.

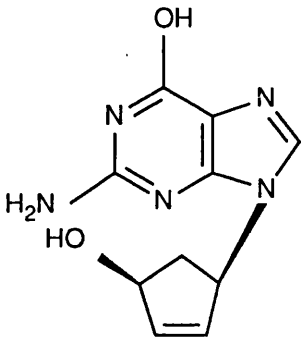
The first step involved a Prins reaction and gave a 50% yield of the combined *cis* diol(**240, 241**). The second key step involved a palladium (O) catalysed reaction[179] with a suitable hetrocyclic base. In this case imidazole was used and the mechanism for the reaction is shown in **scheme 3.4**.

Scheme 3.4

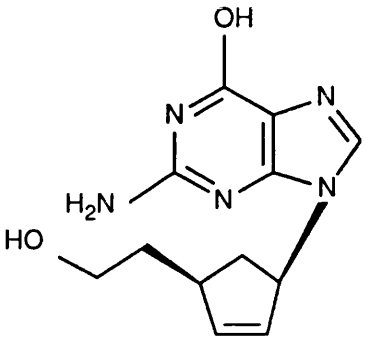


Since carbovir (**224a**) and the one lower homologue of carbovir (**243**) showed high anti viral activity, we decided to prepare the one higher homologue (**244**). The

antiviral activity of such a compound would provide more information about the kind of substrates the HIV reverse transcriptase enzyme would tolerate[180].



(243)



(244)

CHAPTER FOUR

RESULTS AND DISCUSSION

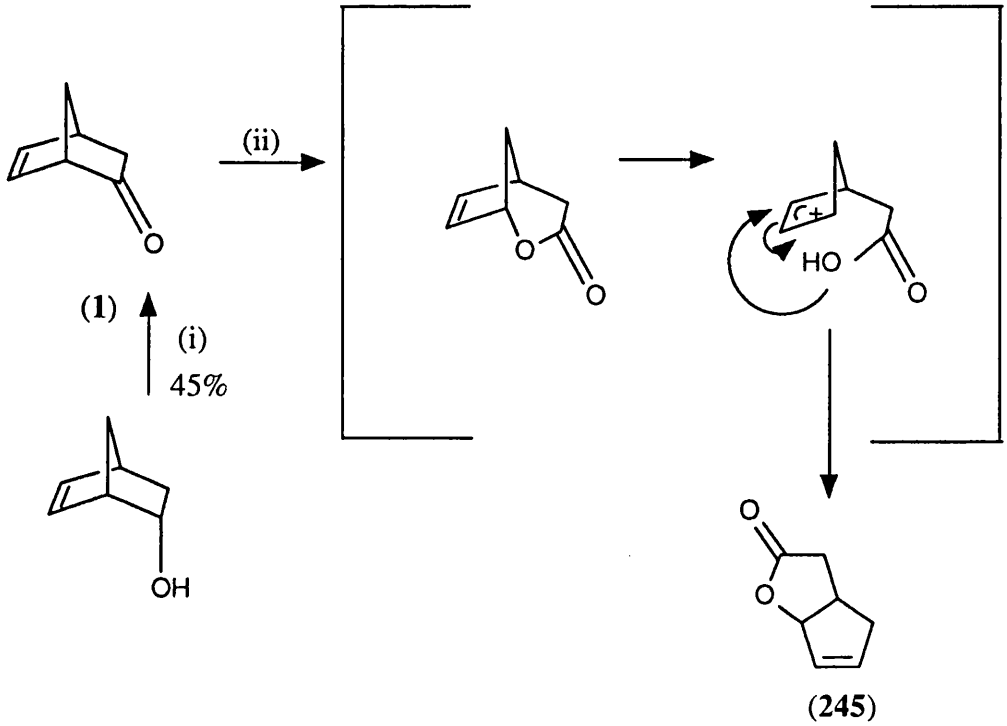
ATTEMPTED SYNTHESIS OF HOMOCARBOVIR

CHAPTER 4

4.0 Attempted synthesis of Homocarbovir (244)

The final step in the preparation of homocarbovir was to be a palladium catalysed reaction of the *cis* diacetate (**247**) with the appropriate heterocycle. The *cis* diacetate was readily prepared in four steps. Norbornenol was oxidised to ketone (**1**) with pyridinium chlorochromate[181]. Baeyer-Villiger oxidation of the ketone (**1**) with trifluoroacetic anhydride and hydrogen peroxide[182]afforded the rearranged lactone (**245**) (**Scheme 4.1**) in 50% yield. Rearrangement of the bridged to the fused lactone is known[182].

Scheme 4.1

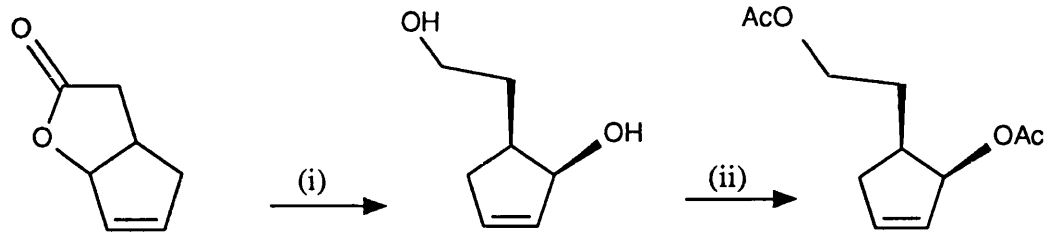


(**245**)

Reagents: (i) PDC, CH_2Cl_2(ii) $(CF_3CO)_2O$, H_2O_2 , CH_2Cl_2, 0°C.

The lactone was reduced to the *cis* diol (**246**) (**scheme 4.2**) with LAH and *bis* acetylated with acetic anhydride and DMAP in pyridine to give the diacetate in 47% yield.

Scheme 4.2

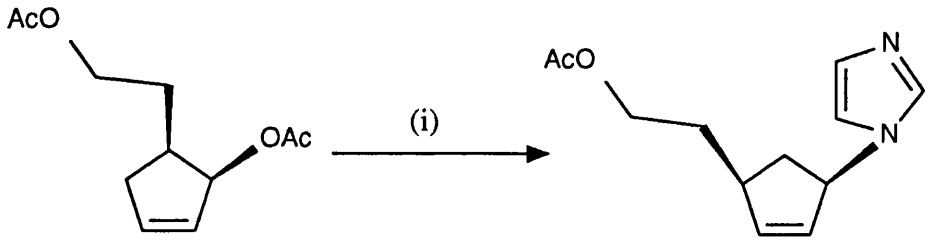


(245) (246) (247)

Reagents: (i) LAH, THF, 0°C; (ii)Ac_2O, DMAP.

To investigate the palladium (O) coupling imidazole was used as the heterocycle, (**Scheme 4.3**). Under the conditions used by Lindell et al[178] imidazole was coupled with the diacetate to give the *cis* compound (**248**). However despite careful chromatography, n.m.r. analysis of the product indicated the presence of more than one compound and it has not been possible to fully characterise (**248**).

Scheme 4.3



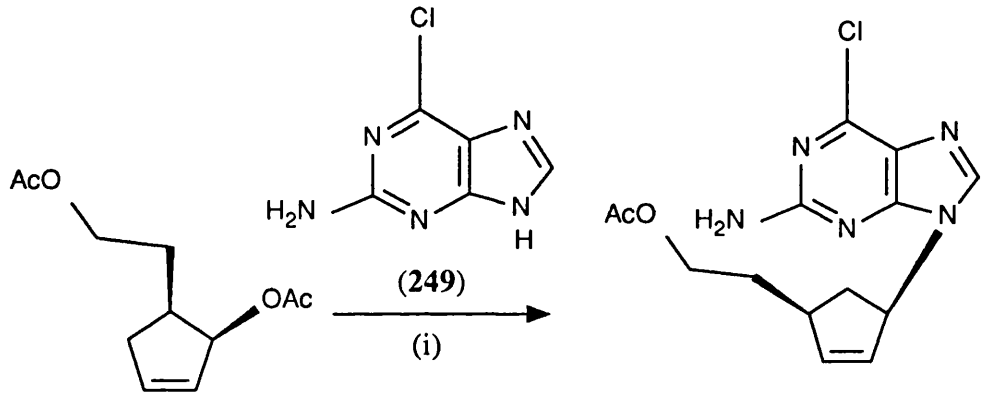
(247) (248)

Reagents: (i) $C_3H_3N_2$, Et_3N, THF, $Pd(Ph_3)_4$, 50°C, 24hr.

Similar conditions were applied to the addition of the amino-chloropurine (**249**). The amino-chloropurine was deprotonated with sodium hydride in DMF/THF

as such a solvent mixture was required due to the poor solubility of the chloropurine **(249), scheme 4.4.** Despite a seemingly clean reaction by tlc it was not possible to identify the product obtained.

Scheme 4.4



(247) **(250)**

Reagents: (i) **249**, NaH, DMF/THF, $Pd(Ph_3)_4$, 50°C, 24hr.

A possible reason for the failure to produce (**244**) maybe due to reaction at the amine of the base instead or as well as the amide. To circumvent this problem the amino chloropurine was reacted with hexamethyldisilazide to afford the triple TMS protected compound. This was used immediately with the *cis* diacetate and the palladium (0) catalyst. No reaction occurred with the protected hetrocycle, possibly indicating that the sensitive TMS had been displaced before the reaction took place.

The amount of material (**247**) and lack of time precluded further investigation of this route.

CHAPTER FIVE

EXPERIMENTAL

CHAPTER 5

Experimental

5.0 Instrumentation and Experimental Techniques

5.1 Solvents and Reagents

Solvents and reagents were dried and purified prior to use according to the procedures described in the "Purification of Laboratory Chemicals"[183]. Petrol refers to petroleum ether boiling range 60-80°C, tetrahyhrofuran and ether were predried over sodium wire and then refluxed over sodium benzophenone ketyl under a nitrogen atmosphere until anhydrous. Osmium tetroxide was used as a solution in ^{t}butanol and prepared according to the procedure of Daniels and Fischer[184]. Water refers to distilled water. Dilute solution refers to 2M unless otherwise stated. Paraformaldehyde was stored over P_2O_5. Gaseous formaldehyde was produced by heating at 120°C in an oil bath with a P_2O_5 trap. After half an hour the trap was removed and a side arm fitted which led to the reaction flask.

5.2 Chromatography

Thin layer chromatography (TLC) was used routinely to monitor the progress and purity of compounds. TLC was performed on Merck DC-alufolien kieselgel 60 F_{254} sheets containing fluorescent indicator. TLC plates were visualized, when possible, by short wavelength (254 nm) ultraviolet light and by treatment with either a solution of anisaldehyde (anisaldehyde (9 cm^3), glacial acetic acid (12.5 cm^3) and conc^n sulphuric acid (6cm^3) in 95% ethanol(300 cm^3) or a 0.5% (w/v) aqueous solution of potassium permanganate, followed by warming of the TLC plate.

Purification of compounds was achieved by medium pressure chromatography[185] using Merck 9385 silica gel. Columns were packed as a slurry in the eluting solvent. Pressure was applied to the column *via* a small hand bellow.

5.3 General

Moisture sensitive reactions were performed in dry glassware (oven 120°C overnight and or flame drying under a positive flow of nitrogen) syringes and stirrer bars were dried and stored over $CaCl_2$.

Solvents were removed with a Buchi rotary evaporator using a water aspirator or a vacuum pump as required and a variable temperature water bath.

5.4 Analysis and Spectroscopy

Melting points (m.p) were determined on Electrothermal MK III or Gallenkamp apparatus and are uncorrected. Elemental micro analysis were carried out using a Carlo Erba 1106 Elemental Analyser.

Infrared spectra were recorded in the range 4000-600 cm^{-1} using a Perkin Elmer 1310 spectrophotometer and peaks are reported (υ_{max}) in wavenumbers (cm^{-1}).

Proton magnetic resonance spectra were recorded on a JEOL GXFT 270 (270 MHz) spectrometer unless otherwise indicated. Carbon-13 magnetic resonance spectra were recorded on a JEOL GXFT 270 spectrometer operating at 67.8 MHz employing 90 and 135 DEPT pulse sequences to aid multiplicity determination. Chemical shifts (δ) are expressed in parts per million downfield from an internal standard, tetramethylsilane. Multiplicities are denoted by s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). The abbreviation br (broadened) is used to indicate significant broadening due to rapid exchange or unresolved fine coupling. 2D homonuclear shift correlated (COSY) spectra were used to confirm proton assignments

where required.

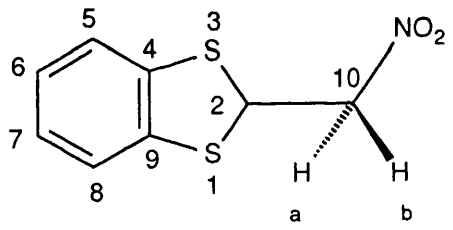
Mass spectra were recorded using a VG analaytical 7070E instrument with a VG 2000 data system. Electron ionisation (E.I.) spectra were produced using an ionising potential of 70 eV, chemical ionisation (C.I.) was performed using isobutane as the reagent gas.

Benzoditholylium Tetrafluoroborate (141)[114]

Anthranilic acid (41.4 g, 0.3 mol) in dioxane (100 cm^3) was added, *via* a dropping funnel, over one hour to a gently refluxing solution of 1,2 dichloroethane (700 cm^3), carbon disulfide (148 cm^3, 2.49 mol), isoamyl alcohol (54 cm^3, 0.5 mol) and isoamyl nitrite (52 cm^3, 0.39 mol) at 70°C in an oil bath. After addition of anthranilic acid the reaction mixture was refluxed for forty minutes. The reaction was allowed to cool to room temperature and the solvents were removed *in vacuo* using a water bath at 50°C. The brown residue was taken up in ether (340 cm^3) and decolourized with activated charcoal and filtered through celite. The resulting orange solution was cooled with stirring at 0°C, tetrafluoroboric acid/ether complex (48 cm^3, 0.94mmol) was added dropwise over fifteen minutes. The grey precipitate formed was collected by filtration under nitrogen to afford the title compound (58 g, 79%), m.p. 144-146^{0}C (acetonitrile/ether) (lit[114] 149°C);δ_H (CD_3CN), 8.1 (2H, m, 6,7-H), 8.8 (2H, m, 5, 8-H), 11.5 (1H, s, 2-H).

Phenylmethylsulfone[118]

Thioanisole (4 g, 32.25 mmol) was dissolved in methylene chloride (30 cm^3) and cooled to 0°C. To this mCPBA (16.3 g, 71 mmol) was added in portions to maintain the



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solutions below 5°C and stirred for a further three hours. The solution was filtered through celite, washed with methylene chloride (50 cm^3) and saturated $NaHCO_3$ (2x 50 cm^3). The organic extracts were combined, dried ($MgSO_4$) and reduced *in vacuo*. The residue was recrystallised from $EtOH/H_2O$ to afford the title compound (1.44 g, 30%), m.p. 84-86°C (Lit[118], 88°C); δ_H3.1 (3H,s, Me), 7.6 93H, m, Ar), 7.9 (2H, m, Ar).

2-Nitromethyl-1,3-benzodithiole (147)

1,3 Benzodithiolylium tetrafluoroborate (**141**) (1.6 g, 6.4 mmol) was dissolved in nitromethane (29.5 cm^3) and cooled with stirring to 0°C . Sodium hydride (178 mg, 7.5 mmol) in tetrahydrofuran (1 cm^3) and nitromethane (0.5 cm^3) was added dropwise *via* syringe to the solution of benzodithiolylium tetrafluoroborate. The solution was stirred at 0°C for thirty minutes. The reaction was quenched by pouring into water (25 cm^3) and extracted with ethyl acetate (2 x 50 cm^3). The combined organic extracts were dried ($MgSO_4$) and solvents removed *in vacuo* to afford the *nitro* compound (1.72 g, 82%) as a brown oil; υ_{max} (CH_2Cl_2/cm^{-1}) 3020, 2990, 1680, 1540 (NO_2), 1360 (NO_2); δ_H ($CDCl_3$) 4.6 (2H, d, *J* 7.5Hz, $10_{a,b}$-H), 5.3 (1H, t, *J* 7.5 Hz, 2-H), 7.15 (2H, dd, *J* 6 and 3 Hz, 6,7-H), 7.3 (2H, dd, *J* 6 and 3 Hz, 5,8-H); δ_C 49 (C-2), 80 (C-10), 123 (C-6,7), 128 (C-5,8), 135 (C-4 and 9); m/z E.I. 213 (M^+, 20%), 166 (60), 153 (100), 134 (40).

2-Diethylphosphinyl-1,3-benzodithiole (149)[122]

1,3-Benzodithiolylium tetrafluoroborate (**141**) (2 g, 8.3 mmol) was dissolved in acetonitrile (40 cm^3) and stirred under nitrogen at room temperature. Triethylphosphite (1.4 cm^3, 8.3 mmol) and sodium iodide (1.2 g, 8.3 mmol) were added consecutively. The solution was stirred for thirty minutes at room temperature. Solvents were removed *in vacuo*, the residue dissolved in water (50 cm^3) and extracted with methylene chloride

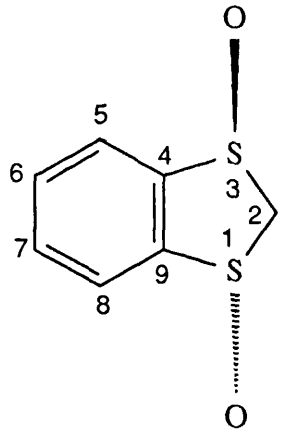
(3 x 50 cm^3). The organic extracts were dried ($MgSO_4$) and solvents removed *in vacuo* to afford the title compound (2.36 g, 98%) as a purple crystalline solid, m.p. 113°C (EtOH) (lit[122] 115°C); δ_H ($CDCl_3$) 1.2 (6H,t, *J* 6.75 Hz, 2xCH_3), 4.2 (4H, m, 2xCH_2), 4.85 (1H, d, $J_{2,PO}$ 6Hz, 2-H), 7.02 (2H, m, 6,7-H), 7.2 (2H, m, 5,8-H).

2-Methylene-1,3-benzodithiole (150)

Phosphonate (**149**) (250 mg, 0.86 mmol) was dissolved in tetrahydrofuran and cooled under nitrogen to -78°C. ^{n}Butyllithium (0.65 cm^3, 1.03 mmol) was added dropwise *via* syringe over ten minutes. The resultant yellow solution was stirred at -78°C for thirty minutes. Paraformaldehyde (52 mg, 1.7 mmol) was added in one portion, stirred at -78°C and allowed to warm to room temperature. The reaction was quenched by addition of 10% 1N hydrochloric acid in ethanol (1 cm^3). Solvents were removed *in vacuo*, the residue preabsorbed on silica and subjected to flash chromatography eluting with 10% methylene chloride and 90% petrol to afford the *title compound* as a red oil; δ_H ($CDCl_3$) 5.6 (2H, s, 10_{ab}-H), 7.0 (2H, m, 6,7-H), 7.2 (2H, , 5,8-H). The compound rapidly decomposed and was not characterized further.

1,3-Benzodithiole (151)[114]

Sodium borohydride (1.62 g, 43 mmol) was suspended in THF (100 cm^3) and cooled to 0°C under nitrogen. To the solution benzodithiolylium tetrafluoroborate (**141**) (10.3 g, 43 mmol) was added in portions so that the temperature remained at 0°C. The solution was stirred at 0°C for one hour. The reaction was quenched by pouring the solution into water (400 cm^3) and crushed ice (100 g). The aqueous layer was extracted with ether (3 x 200 cm^3). The organic layers were combined, dried ($MgSO_4$) and solvents removed *in vacuo* to give a brown oil. The residue was distilled using a Kugelrohr to



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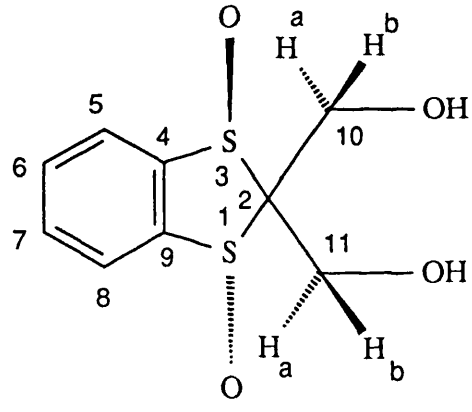
give the title compound (4.5 g; 68%) as a colourless oil b.p. (80°C, kugelrohr 0.3mmHg) (lit[114] 88°C,0.6mmHg); δ_H ($CDCl_3$) 4.5 (2H, s, 2-H), 7.0 (2H, m, 6 ,7-H), 7.2 (2H, m, 5,8-H).

(1RS,3RS)-1,3-Benzodithiole-1,3-dioxide (152)

1,3-Benzodithiole (**151**) (5g, 3.2 mmol) was dissolved in methanol (127 cm^3) and water (10 cm^3). To the reaction mixture sodium periodate (17.4 g, 8.1 mmol) was added in one portion and the suspension stirred for thirty six hours at 50°C. The reaction mixture was allowed to cool to 0°C, diluted with methylene chloride (40 cm^3) and filtered through celite to remove excess periodate. Solvents were removed *in vacuo* and the residue subjected to flash chromatography eluting with 3-7% isopropanol and 97-93% methylene chloride. Four compounds were obtained, the monoxide (**153**), *Trans* dioxide (**152**), *Cis* dioxide (**154**) and sulfone sulfoxide Trioxide (**155**). N.m.r. analysis gave a crude ratio for the reaction as 1.5:6:1:1 respectively. The *monosulfoxide* (**153**) had m.p. 92°C (CH_2Cl_2/ether) (Found C, 49.2; H, 3.48; $C_7H_6S_2O$ requires; C, 49.41; H, 3.53%); δ_H ($CDCl_3$) 4.18 (1H, d, $J_{2a,2b}$ 13.5 Hz, 2_a-H), 4.4 (1H, d, $J_{2b,2a}$ 13.5 Hz, 2_b-H), 7.52 (3H, m, 6,7 and 8-H), 7.9 (1H,d, $J_{5,6}$ 0.75 Hz 5-H); m/z E.I. 170 (M^+, 80%), 153 (20), 140 (100), 121 (20).

The *Trans* dioxide (**152**) (3 g, 50%) had m.p. 136-137°C (CH_2Cl_2/iPr_2O) (Found C, 45.1; H, 3.18; $C_7H_6S_2O_2$ requires C, 45.2; H, 3.2%); δ_H ($CDCl_3$), 4.42 (2H, s, 2-H), 7.84 (2H, m, 6,7-H), 8.0 (2H, m, 5,8-H); δ_C 72 (C-2), 129 (C-6,7), 132 (C-5,8), 145 (C-4,9); m/z E.I. 186 (M^+, 40%), 156 (100).



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(1RS,3RS)-2-[BisHydroxymethyl]-1,3-benzodithiole -1,3-dioxide (156)

Method a

Dioxide (**152**) (983 mg, 5.2 mmol) was dissolved in tetrahydrofuran (15 cm^3) and stirred under nitrogen at 0°C. To the solution lithium diisopropylamide (6.7 mmol) was added over five minutes *via* syringe affording a bright yellow solution of the resultant anion. To the solution, paraformaldehyde (792 mg, 26.4 mmol) was added in one portion and the solution allowed to warm to room temperature over three hours. The reaction was quenched by the addition of acetic acid in tetrahydrofuran (5.9 cm^3, 1.7M) to the vigorously stirring reaction mixture. Solvents were removed *in vacuo*, the residue preabsorbed into silica and subjected to flash chromatography eluting with 8% isopropanol and 92% methylene chloride to afford the *title compound* (800 mg, 62%) as a brown solid m.p. 113°C (methylene chloride/isopropanol) (Found C, 44.1; H, 4.13; $C_9H_{10}S_2O_4$ requires C, 44.0, H, 4.00%); δ_H 3.7 (2H, br *s*, OH), 4.4 (4H, m, $10_{a,b}$,$11_{a,b}$ -H), 7.8 (2H, dd, *J* 6 and 4.5 Hz 6,7-H), 7.9 (2H, dd, *J* 6 and 4.5 Hz, 5,8-H); m/z C.I. 247 ($M^+ + 1$, 95%), 199 (80), 183 (100).

Method b:

Dioxide (**152**) (500 mg, 2.9 mmol) was dissolved in water (21 cm^3) at room temperature. To this paraformaldehyde (435 mg, 14.5 mmol) and K_2CO_3 (400 mg, 2.9 mmol) was added in one portion. After three hours the solution was freeze dried and filtered through a pad of silica and celite eluting with 15% iPrOH/CH_2Cl_2. The *title compound* was afforded (490 mg, 68.7%) as a brown solid. Analysis showed the sample to be identical with the data described above.

(1RS,3RS)-2-Hydroxymethyl-2-methoxymethyl-1,3-benzodithiole-1,3-dioxide (157)

1,3-Benzodithiole-1,3-dioxide (**152**) (25 mg, 0.13 mmol) was dissolved in methanol (1 cm^3) and stirred under nitrogen at room temperature. To the stirred solution potassium carbonate (129 mg, 0.94 mmol) and paraformaldehyde (20 mg, 0.67 mmol) was added in a single portion. The reaction mixture was stirred for twenty four hours. Excess potassium carbonate was removed by filtration through celite eluting with 20% isopropanol and 80% methylene chloride. Solvents were removed *in vacuo* to give a yellow residue which was preabsorbed on silica and subjected to flash chromatography. The *title compound* (15.4 mg, 45%) was afforded as a white solid m.p. 144°C (isopropanol/methylene chloride) (Found: C, 46.0; H, 4.63 $C_{10}H_{12}S_2O_4$ requires C, 46.15; H, 4.61%); υ_{max} (kBr)/cm^{-1} 3400 (OH), 3090, 2990, 2910, 1445, 1380, 1030 (S=O), 950; δ_H ($CDCl_3$) 2.95 (1H, br s, OH), 3.42 (3H, s, OMe), 4.15 (1H, d, $J_{10a,10b}$ 11 Hz, 10_a-H), 4.27 (1H, d, $J_{10b,10a}$ 11 Hz, 10_b-H), 4.37 (1H, d, $J_{11a,11b}$ 13 Hz, 11_a-H), 4.47 (1H, d, $J_{11b,11a}$ 13 Hz, 11_b-H), 7.8 (2H, m, 6,7-H), 7.95 (2H, m, 5,8-H); m/z C.I. 261 ($M^+ + 1$, 20%), 197 (100), 183 (98), 153 (40), 134 (25).

Cis and Trans (1RS)-2-Hydroxymethyl-1,3-benzodithiole-1 -oxide (160 and 161)

Alcohol (**163**) (793 mg, 4.3 mmol) was dissolved in methylene chloride (40 cm^3) and cooled to -78°C under nitrogen. To the solution m- chloroperoxybenzoic acid (1.85 g, 10.77 mmol(50% tech mCPBA)) was added in one portion and the solution stirred at -78°C for two hours. The solution was poured into saturated sodium hydrogen sulphite (30 cm^3) and extracted with methylene chloride (3 x 75 cm^3). The combined organic extracts were dried ($MgSO_4$) and solvents removed *in vacuo*. The residue was subjected to flash chromatography eluting with 5% isopropanol 95% methylene chloride. *Cis* and *trans* diastereomers were readily separated affording the *trans* monoxide (**160**) (204 mg, 24%) as an oil; δ_H ($CDCl_3$) 3.45 (1H, dd, J_{gem} 12 and $J_{10a,2}$ 9

Hz, 10_a-H), 3.85 (1H, dd, J_{gem} 12 and $J_{10b,2}$ 5.3 Hz, 10_b-H), 4.4 (1H, s, OH) 4.7 (1H, dd, $J_{2,10a}$9 and $J_{2,10b}$ 5.3 Hz, 2-H), 7.28 (1H, m, 8-H), 7.46 (2H, m, 6,7-H), 7.86 (1H, d, $J_{5,6}$ 8.3 Hz, 5-H); m/z C.I. 200 (M^+, 100%), 156 (60), 153 (10).*Cis* monoxide (**161**) (98 mg, 11.5%); δ_H ($CDCl_3$) 3.88 (1H, s, OH), 4.24 (1H, dd, J_{gem}12 and $J_{10a,2}$ 4.5 Hz, 10_a-H), 4.44 (1H, dd, J_{gem}12 and $J_{10b,2}$ 9 Hz, 10_b-H), 4.66 (1H, dd, $J_{2,10a}$ 9 and $J_{2,10b}$ 4.5 Hz, 2-H), 7.3 (1H, m, 8-H), 7.46 (2H, m, 6,7-H), 7.8 (1H,d, $J_{5,6}$ 8.3 Hz, 5-H).

(1RS)-2-Methylene-1,3-benzodithiole-1-oxide (162)

2-Hydroxymethyl-1,3-benzodithiole-1-oxide (**160**) (90 mg, 0.45 mmol) was dissolved in methylene chloride (4.5 cm^3) and cooled under nitrogen to 0°C. Triethylamine (315 µl, 2.5 mmol) was added dropwise over five minutes followed by methanesulphonyl chloride (4.5 µl, 0.59 mmol) before the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by pouring into water (50 cm^3) and extracted with methylene chloride (2 x 100 cm^3). The combined organic extracts were dried ($MgSO_4$) and solvents removed *in vacuo*. The residue was subjected to flash chromatography eluting with 5% isopropanol and 95% methylene chloride. The *title compound* was afforded (65.6 mg, 80%) as a colourless oil. δ_H ($CDCl_3$) 6.15 (1H, d, J_{gem} 4.5 Hz, 10_a-H), 6.4 (1H, d, J_{gem} 4.5 Hz, 10_b-H), 7.3-7.6 (3H, m, 6,7,8-H), 7.9 (1H, m, 5-H); m/z C.I. 183 (M^+ + 1, 100%), 160 (30), 149 (30), 140 (40).

2-Hydroxymethyl-1,3-benzodithiole (163)

1,3-Benzodithiole (**151**) (5g, 32.5 mmol) was dissolved in tetrahydrofuran (80 cm^3) and cooled to -78°C with stirring. ^{n}Butyllithium (36.6 cm^3, 58.5 mmol) was added dropwise over five minutes and the solution allowed to stir for fifteen minutes.

Paraformaldehyde (2.9g, 97.5 mmol) was added in one portion and the solution allowed to warm to room temperature over twelve hours. The reaction was quenched by pouring into water (100 cm^3) and extracted with methylene chloride (3 x 100 cm^3). The organic extracts were dried ($MgSO_4$) and solvents removed *in vacuo*. The residue was preabsorbed on silica and subjected to flash chromatography eluting with 30% ethyl acetate and 70% petrol to afford the *title compound* (3.97 g, 66.5%) as a green oil b.p. (215°C, 0.2mmHg); δ_H ($CDCl_3$) 2.15 (1H, br s, OH), 3.7 (2H, d, *J* 9 Hz,$10_{a,b}$-H), 4.8 (1H, t, $J_{2,10}$ 9 Hz, 2-H), 7.0 (2H, m, 6,7-H), 7.2 (2H, m, 5,8-H); δ_C 50 (C-2), 61 (C-10), 118 (C-6,7), 131 (C-9,4); m/z E.I. 184 (M^+, 100%), 153 (70).

(1RS,3RS)-2-Hydroxymethyl-1,3-benzodithiole-1,3-dioxide (158)

2-Hydroxymethyl-1,3-benzodithiole (**163**) (793 mg, 4.3 mmol) was dissolved in methylene chloride (40 cm^3) and cooled to -78°C under nitrogen. Meta chloroperoxybenzoic acid (50%, 1.85 g, 10.7 mmol) was added in one portion and the solution stirred at -78°C for two and a half hours. The reaction was quenched by pouring into sodium hydrogen sulphite (5%, aq, 25 cm^3) and extracted with methylene chloride (3 x 50 cm^3). The organic layers were dried ($MgSO_4$) and solvents were removed *in vacuo*. The residue was subjected to flash chromatography eluting with 5% isopropanol and 95% methylene chloride to afford the *title compound* (316 mg, 40%) as a viscous oil. δ_H ($CDCl_3$) 1.9 (1H, br s, OH), 4.45 (1H, dd, $J_{2,10a}$ 7 and $J_{2,10b}$ 3.7 Hz, 10_a-H), 4.62 (1H, dd, J_{gem} 13.5 and $J_{10a,2}$ 7 Hz, 10a-H), 4.65(1H, dd, J_{gem} 13.5 and $J_{10b,2}$ 3.7 Hz, 10b-H) 7.82 (2H, m, 6,7-H), 8.0 (2H, m, 5 ,8-H); m/z E.I. (M^+, 60%), 156 (100).

(1RS,3RS)-2-N,N'-Dimethylaminomethyl-1,3-benzodithiole-1,3-dioxide (172)

1,3-Benzodithiole-1,3-dioxide (**152**) (1.5 g, 61.7 mmol) was dissolved in water (30 cm^3) and aqueous dimethylamine (34%, aq, 30 cm^3), formalin (37% aq, 904 μl) and concentrated hydrochloric acid (10 drops) were added consecutively. The solution was stirred at 60°C for forty eight hours. The solution was allowed to cool to room temperature, poured into water (50 cm^3) and extracted with methylene chloride (3 x 50 cm^3). The combined organic extracts were dried ($MgSO_4$) and solvents were removed *in vacuo* to afford the *title compound* (1.7 g, 87%) as a white crystalline solid m.p. 142°C (isopropanol/methylene chloride); (Found C, 48.9; H, 5.47; N, 5.6. $C_{10}H_{13}S_2O_2N$ requires C, 49.38; H, 5.35; N, 5.76%); δ_H ($CDCl_3$) 2.2 (6H, s, NMe_2), 3.2 (1H, dd, J_{gem} 13.5 and $J_{10a,2}$ 7.5 Hz, 10_a-H), 3.42 (1H, dd, J_{gem} 13.5 and $J_{10b,2}$ 9 Hz, 10_b-H), 4.2 (1H, dd, $J_{2,10b}$ 9 and $J_{2,10a}$ 7.5 Hz, 2-H), 7.6-7.9 (2H, m, 6,7-H), 8.0 (2H, m, 5,8-H); δ_C 42 (C-NMe_2), 50 (C-10), 81 (C-2), 126 127 (C-6 and 7) 130 132 (C-5 8), quaternary carbon not seen; m/z E.I. 243 (M^+, 7%) 226 (15), 195 (20), 86 (40), 71 (80), 58 (100).

(1RS,3RS)-2-Methylene-1,3-benzodithiole-1,3-dioxide (142)

Amine (**172**) (105 mg, 0.43 mmol) was dissolved in methyl iodide (2 cm^3) and methyl chloride (1 cm^3). After three hours a white precipitate was observed, after a further twelve hours no amine was detected by TLC. Solvents were removed *in vacuo* to afford the title compound along with trimethylammonium iodide. The *title compound* was used without further purification. δ_H ($CDCl_3$) 6.9 (2H, s, 2x10-H), 7.76 (2H, dd, *J* 6 and 3 Hz, 6 ,7-H), 7.98 (2H, dd *J* 6 and 3 Hz, 5,8-H); δ_C 129 (C-6 and 7), 130 (C-5 and 8), 132 (C-10), 142 (C-9 and 4), 159 (C-2); m/z E.I. 198 (M^+, 80%), 156 (100), 108 (88), 69 (58).

(1RS,3RS)-2-Methoxymethyl-1,3-benzodithiole-1,3-dioxide (159)

Amine (**172**) (131 mg, 0.54 mmol) was dissolved in methanol (4 cm^3) and methyl iodide (4 cm^3) and stirred overnight at room temperature. The reaction mixture was filtered through celite and solvents removed *in vacuo* to afford the title compound (94.9 mg, 89%) as a crystalline solid m.p. 142°C (isopropanol/methylene chloride);(Found C,47.0, H, 4.35, $C_9H_{10}S_2O_3$ requires C, 47.0, H, 4.2%); δ_H ($CDCl_3$) 3.5 (3H, s, OMe), 4.24 (1H, dd, J_{gem} 16.5 and $_{10a,2}$ 10.5 Hz, 10a-H), 4.34 (1H, dd, $J_{2,10a}$ 9 and $J_{2,10b}$ 10.5 Hz, 2-H), 4.38(1H, dd, J_{gem} 16.5 and $J_{10b,2}$ 9 Hz 10b-H), 7.8 (2H, m, 6,7-H), 8.0 (2H, m, 5,8-H); δ_C 60 (OMe), 63 (C-10), 84 (C-2), 128, 129 (C-6,7), 136, 138 (C-5,8), 142 (C-4 and 9); m/z E.I. 230 (M^+, 10%), 172 (50), 156 (100), 108 (60).

2-Hydroxymethyl-1,3-dithiane (179)

Ethyl-1,3-dithiane-2-carboxylate (**174**) (4 g, 20.8 mmol) was dissolved in THF (200 cm^3) and cooled to 0°C. Lithium aluminium hydride (871 mg, 22.9 mmol) was added in a single portion and the reaction mixture stirred at 0°C for forty five minutes. The reaction mixture was quenched by rapid addition of ethyl acetate (100 cm^3) and allowed to reach room temperature over one hours. The solution was poured into saturated aqueous sodium potassium tatrate (100 cm^3) and extracted with ethylacetate (2 x 100 cm^3). The combined organic extracts were dried ($MgSO_4$) and solvents removed *in vacuo*. The title compound (3.1 g, 98%) was afforded as a colourless oil; υ_{max} (thin film)/cm^{-1} 3400 (0H), 2910, 1420, 1060 br (S=O), 920. δ_H ($CDCl_3$), 2.0 (2H, m, 4-H), 2.56 (1H, s, OH), 2.7 (2H, m, 5-H), 2.94 (2H, m, 6-H), 3.89 (3H, br s, $2,7_{a,b}$-H); δ_C 25 (C-7), 27 (C-4 and 6), 47 (C-2), 62 (C-5); m/z E.I. (150 (M^+, 30%), 119 (100).

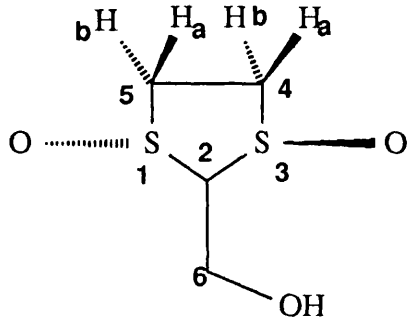
(1RS,3RS)-2-Hydroxymethyl-1,3-dithiane-1,3-dioxide (177)

Method A: Oxidation of (**179**)

2-Hydroxymethyl-1,3-dithiane (**179**) (450 mg, 3 mmol) was dissolved in methanol (7.5 cm^3) and water (0.75 cm^3). Sodium periodate (1.6 g, 7.6 mmol) was added in one portion and the suspension stirred at room temperature for thirty eight hours. The reaction mixture was cooled to 0°C and dimethylsulphide (2 cm^3) was added and stirred four one hour. Ethanol (20 cm^3) was added and solvents removed *in vacuo*. The residue was preabsorbed on silica and subjected to flash chromatography eluting with 10% ethanol, 90% acetone. The *title compound* was afforded (535 mg, 98%) as an inseparable mixture of *cis* and *trans* dioxides (rtio 1.3:1). *Trans* dioxide; (Found C, 33.1; H,5.67 $C_5H_{10}S_2O_3$ requires C,32.96, H,5.5%); υ_{max} (nujol)/cm^{-1} 3100 (OH), 1065 (S=O); δ_H (DMSO-d6), 3.0 (2H, m), 3.1 (1H, m, 2-H), 4.0-4.2 (6H, m), 5.8 (1H, t, *J* 4 Hz, OH); δ_C; m/z C.I. 183 ($M^+ + 1$, 10%), 167 (20), 149 (100), 139 (60). *Cis* dioxide: δ (DMSO d6) 2.4 (2H, m,), 3.0 (2H, m,), 3.4 (3H, m,), 4.2 (2H,), 5.5 (1H, t, 4.9 Hz, OH).

Method b: Reaction of dithiane dioxide with monomeric formaldehyde.

1,3-Dithiane-1,3- dioxide (**189**) (500 mg, 3.28 mmol) was dissolved with warming in pyridine (20 cm^3) and diluted with THF (18 cm^3). The solution was cooled to -78°C under nitrogen and ^{n}BuLi (1.4 cm^3, 3.6 mmol) was added dropwise over ten minutes. After fifteen minutes monomeric formaldehyde[150] (8.2 cm^3, 0.6M, 4.9 mmol) was added *via* syringe. After one hour a small amount of dioxide (**189**) remained and the reaction was quenched with a solution of 2N HCl (8 cm^3) in THF (75 cm^3). Solvents were removed *in vacuo* and the residue subjected to flash chromatography eluting with 10% MeOH and 90% CH_2Cl_2. The fractions containing the *title compound* were washed with dilute aqueous NH_3 (20 cm^3). The organic extract was taken up in ethanol and filtered. The mother liquor was subjected to flash chromatography. *The title compound* was afforded (43 mg, 72%) as a brown solid. Spectroscopic analysis proved



(178)

identical with the sample of *trans* alcohol (**177**) described above.

(1RS,3RS)-2-Hydroxymethyl-1,3-dithiolane-1,3-dioxide (178)

Alcohol (**180**) (8.6 g, 62 mmol) was dissolved in methanol (300 cm^3) and water (30 cm^3). Sodium periodate (29 g, 136.4 mmol) was added in one portion and the solution stirred at room temperature for twenty four hours. The reaction was quenched by the addition of dimethylsulfide (2 cm^3) at 0°C, the solution stirred for a further thirty minutes after which no oxidant remained (starch iodine paper). The solution was filtered through celite and washed with cold methanol (15 cm^3). Excess dimethylsulphide and solvent was removed *in vacuo*. The residue was preabsorbed on silica and subjected to flash chromatography eluting with 10% methanol and 90% methylene chloride to afford the *title compound* (5 g, 48%) as a crystalline solid m.p. 125°C (ethanol) (Found C, 28.6; H, 4.94; $C_4H_8O_3S_2$ requires C, 28.57; H, 4.76%); υ_{max} (crystal)/cm^{-1} 3342 (OH), 2985, 2916, 1427, 1403, 1285, 1159, 1136, 1099, 1018 (S=O); δ_H (DMSO d6) 3.4-3.9 (4H, m, $4_{a,b}$,$5_{a,b}$-H), 4.0 (2H, m, $6_{a,b}$-H), 4.1 (1H, m, 5 Hz, 2-H), 5.5 (1H, t, *J* 7.7 Hz OH); δ_C 300 MHz DMSO) 40, 41 (C-4 and 5), 50 (C-6), 87 (C-2); m/z E.I. 168 (M^+, 45%), 149 (19), 108 (60), 90 (78).

(1RS,3RS)-2-Methylene-1,3-dithiane-1,3-dioxide (186)

2-Hydroxymethyl-1,3-dithane-1,3-dioxide (**177**) (500 mg, 2.7mmol) (as a 1:1 mixture of *cis* and *trans* dioxides) was dissolved in acetonitrile (30 cm^3). To the stirred solution triethylamine (431 cm^3, 3.0mmol) was added *via* syringe. The solution was stirred for ten minutes followed by the addition of disuccinimdyl carbonate (773mg, 3.0 mmol) was added in one portion. After three hours no alcohol was detected by TLC, solvents were removed *in vacuo* and the residue preabsorbed on silica. The preabsorbed residue was subjected to flash chromatography eluting with acetone. The *cis* and *trans* dioxide

were readily separated as colourless oils. *Trans* dioxide (281 mg,63%) ; υ_{max} (thin film)/cm^{-1} 3025, 2990, 2960, 1700, 1420, 1360, 1045 (S=O); δ_H ($CDCl_3$) 2.8 (2H, m, 5a,b-H), 3.05 (2H, m, 4a, 6b-H), 3.15 (2H, m, 4b, 6a-H), 6.4 (2H, s, 7a,b-H); δ_C 15 (C-5), 25 (C-4), 52 (C-6), 122 (C-7), 155 ((C-2); m/z E.I. 164 (M^+, 10%) 116 (100), 58 (60), 41 (70) (Found 163.99818; $C_5H_8O_2S_2$ requires 163.99657) *Cis* dioxide (**187**) dehydration product was also obtained; δ_H ($CDCl_3$) 2.0 (1H, m, 5a-H), 2.6 (1H, m, 5b-H), 2.8 (2H, m, 4a, 6a-H), 3.6 (2H, , 4b and 6b-H), 6.5 (2H, s, 7a and b-H) δ_C 13 (C-8), 24 (C-4), 52 (C-6), 119 (C-7), 158 (C-2).

(1RS,3RS)-2-Methylene-1,3-dithiolane-1,3-dioxide (184)

The dithiolane alcohol (**180**) (200 mg, 1.2 mmol) was dissolved in acetonitrile (12 cm^3) with gentle heating. To the stirred solution 1-cyclohexyl-1-3- (-2-morpholinoethyl) carbodiimide metho-p-toluenesulfonate (710 mg, 1.7 mmol) and copper (II) chloride (80.4 mg, 0.6 mmol) were added consecutively. After one hour a yellow precipitate was formed and after a further three hours no alcohol (**180**) was observed by TLC. The solution was filtered and concentrated *in vacuo* to one third of its original volume (4 cm^3). The concentrated solution was added to a florisil column and eluted with acetonitrile to afford the *title compound* (100 mg, 55%) as a white solid. The dienophile was used immediately. υ_{max} ($CHCl_3$)/cm^{-1} 2980, 1395, 1035 (S=O); δ_H ($CDCl_3$) 3.7 (4H, m, $4_{a,b}$,$5_{a,b}$-H), 6.9 (2H, s, 2x6-H); δ_C (DMSO) 25 (C-4), 50 (C-5), 135 (C-6), 172 (C-2); m/z E.I. 150 (M^+, 80%) 122 (40), 108 (68), 58 (100).

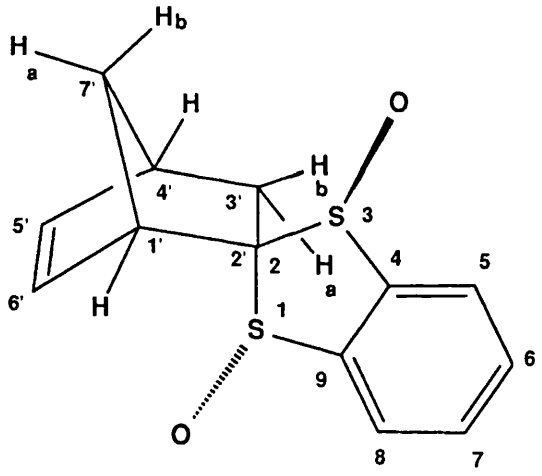
(1RS,3RS,1'RS,4'RS)-Spiro{1,3-Benzodithiole-2,2 'norborn-5'-ene}-1,3-doxide (196)

GENERAL PROCEDURE A:

Amine (**172**) (100 mg, 0.42 mmol) was dissolved in methyl iodide (2 cm^3) and stirred at room temperature over twelve hours. Excess methyl iodide was removed *in vacuo* and the dienophile used without further purification. The dienophile was dissolved in solvent (2 cm^3), freshly distilled cyclopentadiene (129 µl, 2.16 mmol) and added *via* syringe. After the dienophile had been consumed the solution was poured into water (20 cm^3) and extracted with methylene chloride (2 x 50 cm^3). The combined organic extracts were dried ($MgSO_4$) and solvents were removed *in vacuo*. The residue was preabsorbed on silica and subjected to flash chromatography eluting with 5% isopropanol 95% methylene chloride. The *title compound* was afforded a white crystalline solid, as an inseparable mixture of diastereomers.

GENERAL PROCEDURE B:

Amine (**172**) (100 mg, 0.42 mmol) was dissolved in methyl iodide (5 cm^3) and stirred at room temperature for twelve hours. Excess methyl iodide was removed *in vacuo* and the dienophile used without further purification. The dienophile was dissolved in methylene chloride (6 cm^3) and cooled to -78°C under nitrogen. To this Lewis acid (0.45 mmol) was added in one portion. The reaction mixture was stirred at -78°C for fifteen minutes, freshly distilled cyclopentadiene (269 µl, 3.28 mmol) was added *via* syringe. The reaction mixture was stirred until no dienophile remained. The reaction was quenched by the addition of dilute sodium hydroxide. The reaction was allowed to warm to room temperature, poured into water (50 cm^3) and extracted with methylene chloride (2 x 35 cm^3). The combined organic extracts were dried ($MgSO_4$) and solvents were removed *in vacuo*. The *title compound* was afforded as a white solid. The white solid was preabsorbed into silica and subjected to flash chromatography



(196)

eluting with 5% isopropanol and 95% methylene chloride,

Aqueous lithium perchlorate catalysed Diels-Alder reactions

General procedure A was followed using 2.5M aqueous lithium perchlorate. The reaction mixture was stirred at room temperature for thirty minutes. The *title compound* was afforded (69.3 mg, 62%) as an inseparable mixture of diastereomers in a ratio of 8:1.

Diels-Alder reactions in trifluoroethanol

General procedure A was followed using trifluorethanol as the reaction solved. The solution was stirred for three hours at room temperature. The *title compound* was afforded (83 mg, 77%) as an inseparable mixture of diastereomers in a 9.5:1 ratio.

Diels-Alder reaction with boron trifluoroetherate

General procedure B was followed using boron trifluoroetherate as the Lewis acid (55 µl, 0.45 mmol). The *title compound* was afforded (81 mg, 74%) as an inseparable mixture of diastereomers in a 14:1 ratio.

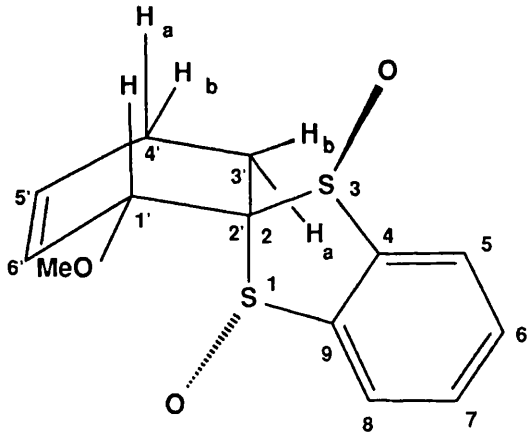
The major diastereomer was obtained in pure form from a single recrystallization from THF m.p. 204°C; (Found C, 59.4; H, 4.54; $C_{13}H_{12}S_2O_2$ requires C, 59.1; H, 4.34): δ_H (400 MHz; $CDCl_3$ 1.7 (1H, m, 7′$_a$-H), 1.75 (1H, dd J_{gem} 12.5 and $J_{3'b,4}$3.3 Hz, 3′$_b$-H), 2.00 (1H, d, J_{gem} 8.3 Hz, 7′$_b$-H), 2.07 (1H, dd, J_{gem} 12.5 and $J_{3'a,4}$ 3.3 Hz, 3′$_a$-H), 3.15 (1H, br s, 4′-H), 3.9 (1H, br s, 1′-H), 6.25 (1H, br s, 5′-H), 6.5 (1H, dd, 6′-H), 7.8 (4H, m, 5,6,7,8-H); δ_C 28 (C-7′), 43 (C-4′), 50 (C-3′), 57 (C-1′), 118 (C-6,7), 120 (C-5′), 122 (C-5,8), 124 (C-6′), 133 (C-4,9); m/z E.I. 264 (M^+, 6%), 185 (18), 156 (100), 140 (30).

(1RS,3RS,1'RS,4'RS)-{Sprio-1,3-benzodithiole 2,2'-oxanorborn-5'-ene}-1,3-dioxide (200)

Amine (**172**) (100 mg, 0.42 mmol) was dissolved in methyl iodide (5 cm^3) and stirred at room temperature under nitrogen for twelve hours. Excess methyl iodide was removed *in vacuo* to give a white solid. The residue was dissolved in methylene chloride (5 cm^3) and cooled to -78°C with stirring under nitrogen. To the solution tin(IV) chloride (97 µl, 0.82 mmol) was added *via* syringe followed by furan (246 µl, 3.28 mmol) and the solution was maintained at -78°C for a further hour. The reaction was quenched by the addition of sodium hydroxide (350 mg in 95% ethanol (1cm^3)), the solution was allowed to warm to room temperature. The reaction mixture was poured into brine (50cm^3) and extracted with methylene chloride (3 x 50cm^3). The combined organic extracts were dried ($MgSO_4$) and removed *in vacuo* to afford the *title compound* (105.2 mg, 97%) as an inseparable mixture of diastereomers in a 6:1 ratio.

Major diastereomer (**200**); υ_{max} (CH_3Cl_3)/cm^{-1} 3080, 2950, 1480, 1120, 1070 (S=O), 1040, 920; δ_H ($CDCl_3$) 1.85 (1H, dd, J_{gem} 13 and $J_{3'b,4}$ 4.5 Hz, 3'$_b$-H), 2.1 (1H, d, $J_{3'a,4}$ 13 Hz, 3'$_a$-H), 5.3 (1H, br s, 4'-H), 6.0 (1H, br s, 1'-H), 6.6 (1H, dd, $J_{5',6'}$ 6 and $J_{5',4'}$ 1.5 Hz, 5'-H), 6.7 (1H, dd, $J_{6',5'}$ 6 and $J_{6',1'}$ 1.5 Hz, 6'-H), 7.8-8.0 (4H, m, 5,6,7,8-H); m/z C.I. 267 (M^+ + 1, 6%) 239 (8), 199 (100), 183 (40).

Minor diastereomer (**201**): δ_H ($CDCl_3$) 1.85 (1H, dd, J_{gem} 13 and $J_{3'b,4}$ 4.5 Hz, 3'$_b$-H), 2.1 (1H, d, $J_{3'a,4}$ 13 Hz 3'$_a$-H), 5.3 (1H, br s, 4'-H), 5.9 (1H, br s, 1-H), 6.75 (1H, dd, $J_{5',6'}$ 6 and $J_{5',4'}$ 3 Hz, 5'-H), 6.9 (1H, dd, $J_{6',5'}$ 6 and $J_{6',1'}$ 3 Hz 6'-H), 7.8-8.0 (4H, m, 5,6,7,8-H).



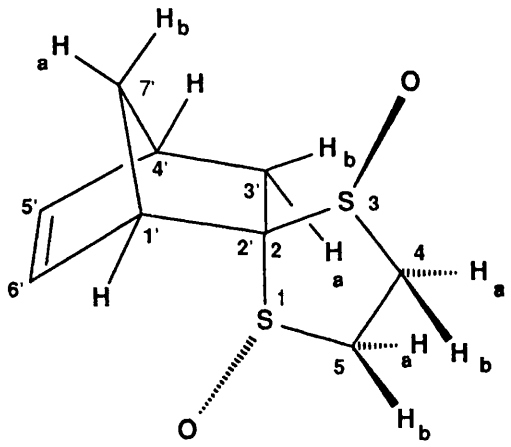
(204)

(1RS,3RS,1'RS)-{sprio-1,3-benzodithiole-2,2'-1'-methoxycyclohex-5'-ene}-1,3-dioxide (204)

Amine (**172**) (100 mg, 0.41 mmol) was dissolved in methyl iodide (5 cm^3) and stirred at room temperature for twelve hours. Excess methyl iodide was removed *in vacuo* to afford 2-methylene-1,3-benzodithiole-1,3-dioxide (**142**) which was used without further purification. The residue was dissolved in methylene chloride (5 cm^3) and stirred at room temperature under nitrogen. 1-Methoxy-1,3-butadiene (290cm^3, 2.87 mmol) was added *via* syringe. After twenty four hours solvent and excess diene were removed *in vacuo* to afford the *title compound*, a single diastereomer as a white solid (89 mg, 77%) m.p. 139-140°C (CH_2Cl_2/THF);(Found C, 55.0, H, 5.16, $C_{13}H_{14}S_2O_3$ requires C, 55.3, H, 5.0%); υ_{max} ($CHCl_3$)/cm^{-1} 3020, 2940, 1440, 1090, 1070 (S=O) 290; δ_H ($CDCl_3$) 1.85 (1H, ddd, J_{gem} 14, $J_{3'a,4'b}$ 12 and $J_{3'a,4'a}$ 6 Hz, 3'$_a$-H), 2.2 (1H, m, 4'$_a$-H), 2.5 (1H, m, 4'$_b$-H), 2.7 (1H, m, 3'$_b$-H), 3.2 (3H, s, OMe), 4.6 (1H, br s, 1'-H), 6.0 (2H, m, 5',6'-H), 7.6-8.0 (4H, m, 5,6,7,8-H); δ_C 20 (C-3'), 22 (C-4'), 58 (OMe), 70 (C-1'), 88 (C-2'), 122 (C-5'), 127 (C-6 and 7), 131 (C-6'), 135 (C-5), 136 (C-8), 142 (C-4), 145 (C-9); m/z E.I. 282 (M^+, 4%), 250 (5), 185 (20), 156 (30), 110 (100).

(1RS,3RS,1'RS,4'RS)-{Spiro- 1,3-dithiolane-2-2'-norborn-5'-ene}-1,3 dioxide (205)

2-Methylene-1,3-dithiolane dioxide (**184**) (130 mg, 0.86 mmol) was dissolved in dichloromethane (4 cm^3) and cooled to -78°C under nitrogen. To the reaction mixture boron trifluoroetherate (197 µl, 1.6 mmol) was added *via* syringe. After fifteen minutes freshly distilled cyclopentadiene (570 µl, 0.93 mmol) was added and the solution stirred at -78°C for thirty minutes. The reaction was quenched by rapid addition of ethanolic sodium hydroxide (3.5 g/100 cm^3, 2 cm^3). The solution was poured into water (10 cm^3) and extracted with dichloromethane (3 x 50 cm^3). The combined



(205)

organic extracts were dried ($MgSO_4$) and subjected to flash chromatography eluting with 10% MeOH and 90% CH_2Cl_2 to afford the *title compound* as a single diastereomer (132 mg, 70%), m.p. 142°C (Found: C, 50.00; H, 5.65. $C_9H_{12}S_2O_2$ requires C, 50.00; H, 5.56%); υ_{max} ($CHCl_3$)/cm^{-1} 3010, 1240, 1050 (S=O); δ_H ($CDCl_3$) 1.8-2.0 (3H, m, 3′$_b$ 7′$_a$ and 7′$_b$-H), 2.19 (1H, dd, J_{gem} 13 and $J_{3'a,4'}$ 8 Hz, 3′$_a$-H), 3.25 (1H, br s, 4′-H), 3.4-3.5 (4H, m, 4′$_{ab}$,5$_a$ and 1′-H), 4.0 (1H, m, 5$_b$-H), 6.25 (1H, dd $J_{5',6'}$ 6.5 and $J_{5',4'}$ 3.7 Hz, 5′-H), 6.5 (1H, dd, $J_{6',5'}$ 6.5 and $J_{6',1'}$ 3.7 Hz, 6′-H); δ_C 29 (C-7′), 42 (C-4′), 45 (C-1′), 49 (C-4), 50 (C-3′), 51 (C-5), 98 (C-2′), 132 (C-5′), 141 (C-6′); m/z E.I. 217 (M^+ + 1, 35%), 108 (40), 91 (77), 60 (100).

(1RS,3RS,1′RS,4′RS)-{Spiro-1,3-dithiane-2,2′-norborn-5′-ene}-1,3-dioxide (206)

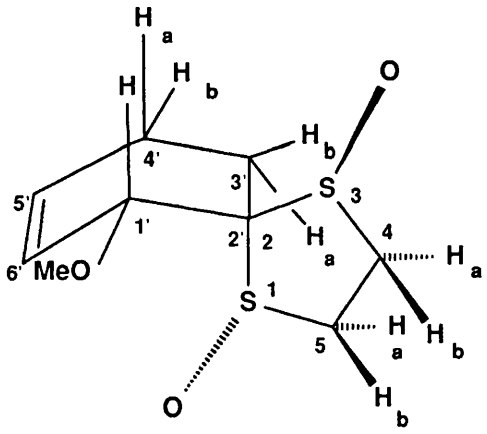
2-Methylene-1,3 dithiane-1,3-dioxide (**186**) (58 mg, 0.35 mmol) was dissolved in methylene chloride (5 cm^3) and cooled to -78°C under nitrogen. To this boron trifluoroetherate (82 µl, 0.67 mmol) was added *via* syringe. The solution was maintained at -78°C for fifteen minutes. Freshly distilled cyclopentadiene (233 µl, 2.83 mmol) was added in one portion. The solution was stirred at -78°C for one hour after which no dienophile was detected by TLC. To the reaction mixture sodium hydroxide in fifty percent aqueous ethanol (3.5 mg/cm^{-3}, 3 cm^3) was added and the solution allowed to warm to room temperature. The reaction mixture was poured into water (10 cm^3) and extracted with methylene chloride (3 x 25 cm^3). Solvents were dried ($MgSO_4$) and removed *in vacuo*. The *title compound* (64mg, 80%) was afforded as a single diastereomer m.p. 174-175°C (THF); υ_{max}/cm^{-1} 2999, 1300, 1400 and 1020 (S=O); δ_H ($CDCl_3$) 1.6 (1H, m, 7′a-H), 1.95 (1H, dd *J* 5.9 and *J* 1.6 Hz, 3′b-H), 2.1 (3H, m, 3a, 7′$_b$-H), 2.5 (2H, m,), 3.0 (1H, m), 3.2 (3H, m), 3.35 (1H, m), 3.5 (1H, br *s*, 1′-H), 6.15 (1H, dd *J* 2.6 and *J* 1.3 Hz, 5′-H), 6.45 (1H, dd, *J* 2.6 and *J* 1.3 Hz, 6′-H); δ_C 11, 30, 42, 44, 45, 48, 49, 132, 142; m/z C.I. 231 (M^+ + 1, 80%) 215 (18), 197 (18), 100 (100); Found 230.04200, $C_{10}H_{14}O_2S_2$ requires 230.04352.

(1RS.3RS,1'RS,4'RS)-{Spiro 1,3 dithiolane-2,2'oxanorborn-5'-ene}-1,3-dioxide (213)

2-Methylene-1,3-dithiolane (**184**) (106 mg, 0.7 mmol) was dissolved in methylene chloride (8 cm^3) and cooled to -78°C under nitrogen. To the solution tin (IV) chloride (189 µl, 1.6 mmol) was added dropwise *via* syringe and the solution stirred for fifteen minutes. Freshly distilled furan (420 µl, 5.6 mmol) was added in one portion and the solution stirred at -78°C for one hour. To the reaction mixture TMEDA (240 µl, 1.6 mmol) was added to the solution at -78°C and the solution allowed to reach room temperature over two hours. The precipitate formed was filtered through celite and florisil. The filter cake was washed with methylene chloride (10 cm^3). Solvents were removed *in vacuo* and the residue subjected to flash chromatography eluting with 10% methanol and 90% methylene chloride. The *title compound* was afforded (137mg, 90%) as an inseparable mixture of diastereomers in a 5:1 ratio as a solid.

Major diastereomer; (Found C, 40.0, H, 4.43, $C_8H_{10}S_2O_3$ requires C, 44.0, H, 4.35%); δ_H 2.0 (1H, dd, J_{gem} 11.3 and $J_{3'b,4'}$ 4.5 Hz, $3'_b$-H), 2.2 (1H, d, J_{gem} 11.3 Hz, $3'_a$-H), 3.4-3.8 (3H, m, $4_{a,b}$ 5_a-H), 4.1 (1H, m, 5_b-H), 5.35 (1H, br s 4'-H), 5.6 (1H, br s, 1'-H), 6.6 (1H, dd, $J_{5',6'}$ 6 and $J_{5',4'}$ 1.5 Hz, 5'-H), 6.7 (1H, dd $J_{6',5'}$ 6 and $J_{6',1'}$ 1.5 Hz, 6'-H); δ_C 27, 28, 52, 77, 79, 96, 134, 140; m/z E.I. 218 (M^+, 7%) 190 (10), 150 (20), 124 (50), 68 (100).

Minor diastereomer; δ_H ($CDCl_3$) 1.5 (1H, d, J_{gem} 11.3 Hz $3'_a$-H), 2.8 (1H, dd, J_{gem} 11.3 and $J_{3'b,4'}$ 4.5 Hz, $3'_b$-H), 3.4-3.8 (3H, m, $4_{a,b}$ 5_a-H), 4.1 (1H, m, 5_b-H), 5.21 (1H, br s, 4'-H), 5.35 (1H, br s, 1'-H), 6.7 (2H, m, 5' and 6'-H); δ_C 25, 34, 50, 80, 82, 86, 125, 129.



(210)

(1RS,3RS,1'RS,4'RS)-{Spiro-1,3-dithiolane-2,2'-1'-methoxy cyclohex-5'-ene}-1,3-dioxide (210)

2-Methylene-1,3-dithiolane-1,3-dioxide (**184**) (100 mg, 0.66 mmol) was dissolved in methylene chloride (4 cm^3). To this 1-methoxybutadiene (435 µl, 5.28 mmol) was added dropwise *via* syringe. The solution was stirred for twelve hours at room temperature. Solvents and excess reagents were removed *in vacuo* and the residue subjected to flash chromatography eluting with 10% MeOH and 90% CH_2Cl_2. The *title compound* was afforded as a single diastereomer (114 mg, 74%) as a white crystalline solid m.p. 140°C (THF);(Found C, 47.3, H, 6.15 $C_9H_{14}S_2O_3$ requires C, 46.17, H, 6.0%); δ_H ($CDCl_3$) 2.2-2.6 (4H, m, $3'_{a,b}$and $4'_{a,b}$-H), 3.4 (3H, s, OMe), 3.5 (2H, m, $4_a$and 5_b-H), 3.6 (2H, m, 4_b and 5_a-H), 4.2 (1H, br s, 1'-H), 6.0 (2H, m, 5' and 6'-H); δ_C 22 (C-3'), 23 (C-4', 49 (C-4), 52 (C-5), 56 (C-OMe), 71 (C-1'), 92 (C-2), 124 (C-5'), 129 (C-6'); m/z E.I. 234 (M^+, 10%), 158 (10), 110 (100), 79 (40).

(1RS,1'RS,4'RS)-{Spiro-1,3-benzodithiole-2,2'-norborn-5'-ene}-1-oxide (211)

The spirocyclic *bis* sulphoxide (**196**) (10 mg, 0.04 mmol) was dissolved in acetic acid (1.5 cm^3) and a solution of titanium (III) chloride (30% aq, 45 µl, 0.083mmol) added *via* syringe, the solution was stirred at room temperature under nitrogen for one hour. The reaction mixture was made slightly alkaline with sodium hydroxide poured into brine (10 cm^3) and extracted with ether (3 x 30 cm^3). The combined organic extracts were dried ($MgSO_4$) and solvents removed *in vacuo*. The yellow residue was preabsorbed on silica and subjected to flash chromatography eluting with 5:1, hexane : ether. Bissulfide (**213**) (1.4 mg, 15%) was eluted followed by the *title compound* (**211**): major diastereomer (2.4 mg, 25%) as an oil. δ_H ($CDCl_3$) 1.4 (1H, m), 1.5 (2H, m), 2.2 (1H, m), 3.2 (1H, br s), 3.7 (1H, br s), 6.2 (1H, m), 7.4 (3H, m, Ar), 7.8 (1H, m, Ar); m/z E.I. 248 (M^+, 20%), 206 (25), 166 (100), 140 (20), 107 (20), 80 (40); (Found

248.02903. $C_{13}H_{12}OS_2$ requires 248.03296).

Minor diastereomer. δ_H ($CDCl_3$) 1.5 (2H, m), 2.05 (1H, m), 2.2 (1H, m), 2.6 (1H, br s), 3.05 (1H, br s), 6.0 (1H, m), 6.4 (1H, m), 7.2 (3H, m), 7.8 (1H, m).

(1'RS,4'RS)Spiro-1,3-benzodithiole-2,2'-norborn-5'-ene (213)

Dioxide (**196**) (20 mg, 0.08 mmol) was dissolved in ethanol (1 cm^3) with gentle warming. To the solution titanium (III) chloride (30% aq, 8.3 µl, 0.17 mmol) was added dropwise *via* syringe over two minutes. The resulting yellow solution was stirred for ten minutes. Water (5 cm^3) was added to the reaction mixture followed by 5% sodium hydroxide (2 cm^3). The mixture was poured into water (10 cm^3) and extracted with methylene chloride (2x30 cm^3). The combined extracts were dried ($MgSO_4$). The residue was subjected to flash chromatography eluting with 5:1 hexane : ether. The *title compound* was afforded (8.3 mg, 47%) as a waxy solid. δ_H ($CDCl_3$) 1.65 (2H, br s, $7'_{a,b}$-H), 1.85 (1H, br d, J_{gem} 13.5 Hz, $3'_a$-H), 2.25 (1H, dd, J_{gem} 13.5 and $J_{3'b,4}$ 3 Hz, $3'_b$-H), 2.95 (1H, br s, 4'-H), 3.2 (1H, br s, 1'-H), 6.2 (1H, dd, $J_{5',6'}$ 5.3 and $J_{5',4'}$ 3 Hz, 5'-H), 6.32 (1H, dd, $J_{6',5'}$ 5.3 and $J_{6',1'}$ 3 Hz, 6'-H), 7.5 (4H, m, Ar) *(4H*; m/z E.I. 232 (M^+, 9%), 166 (100).

Further elusion gave the monosulphoxide (**210**) (4.2 mg, 22%), as a five to one mixture of diastereomers. The sample has identical spectroscopic properties as (**210**), prepared as described above.

(1'RS,4'RS)Spiro 1,3-dithiolane-2,2'-norborn-5'-ene (214)

Dioxide (**184**) (50 mg, 0.23 mmol) was dissolved in methylene chloride (4 cm^3) and cooled to 0°C under nitrogen. To the solution, phosphorous tribromide (47 µl, 0.49 mmol) was added *via* syringe over five minutes. The solution was stirred for five

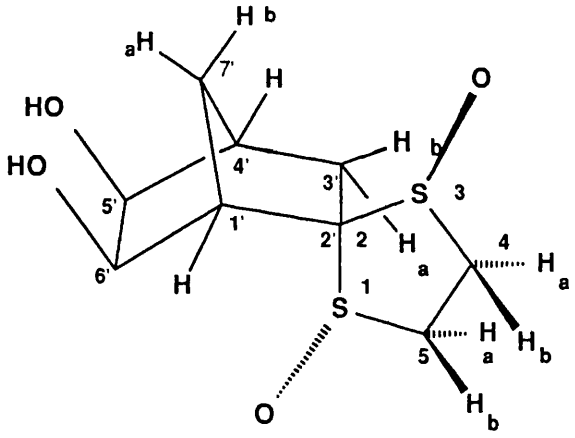
minutes. Water (1 cm^3) was added to the reaction mixture and stirred for five minutes. The reaction was poured into water (10 cm^3) and extracted with methylene chloride (2x 30 cm^3). Solvents were dried (Na_2SO_4) and removed *in vacuo*. The oily residue was preabsorbed on silica and subjected to flash chromatography eluting with 5:1 hexane : ether to afford the *title compound* (38 mg, 91%) as a crystalline solid m.p. 59-60°C (EtOAc); δ_H ($CDCl_3$) 1.67 (2H, br s, 1′ and 4′-H), 1.9 (1H, dd, *J* 12.6 and *J* 2.5 Hz 3′a-H), 2.4 (1H, dd, *J* 12.6 and *J* 3.75 Hz 3′b-H), 2.9 (1H, br *s*, 7′b-H), 2.95 (1H, br s, 7′a-H), 3.2-3.4 (4H, m, 4 and 5), 6.2 (1H, dd, *J* 5.25 and *J* 3 Hz, 5′-H), 6.3 (1H, dd, *J* 5.25 and *J* 3 Hz, 6′-H); δ_C 40 (C-7′), 41 (C-3′), 43 (C-4′), 48 (C-4), 50 (C-5), 57 (C-1′), 135 (C-5′), 140 (C-6′).

Norborneneone (1)[165]

Disulfide (**215**) (49 mg, 0.27 mmol) was dissolved in acetonitrile (4 cm^3) and water (1 cm^3). To the solution calcium carbonate (108 mg, 1.08 mmol) and methyl iodide (180 µl, 2.7 mmol) were added consecutively and the reaction mixture was stirred for forty eight hours when disulfide was not detected by TLC. The reaction mixture was poured into water (60 cm^3) and extracted with ether (3 x 30 cm^3). The combined organic extracts were dried (Na_2SO_4) and removed *in vacuo*, water bath 10°C. The title compound was afforded as a colourless oil (12mg,45%) b.p.70-80 °C 20 mmHg (Lit[165] 110-120 25 mmHg); υ_{max} (thin film)/cm^{-1} 3020, 2995, 1750 (C=O); δ_H($CDCl_3$) 1.8 (3H, m, 3_a, 3_b and 7_a-H), 2.4 (1H, m, 7_b-H), 3.0 (1H, br, dd *J* 3.75 and *J* 1.5 Hz, 4-H), 3.4 (1H, br s, 1-H), 6.1H, dd, *J* 5.6 and *J* 3 Hz 5-H), 6.6 (1H, dd, *J* 5.6 and *J* 3 Hz, 6-H).

Method b: Oxidation of norborneneol

Norborneneol (5g, 45.5mmol) was dissolved in methylene chloride (50cm^3) at room temperature. To the rapidly stirred solution pyridinium dichromate (18.8g, 50mmol) was added in one portion followed by pyridinium trifluroacetate (3g). The



(215)

solution was stirred for thirty six hours after which no alcohol was present. The reaction mixture was diluted with ether ($100cm^3$) and filtered through celite. The filtrate was washed with water ($3x50cm^3$), the organic extracts combined, dried ($MgSO_4$) and the solvents removed *in vacuo*. The brown residue was subjected to flash chromatography eluting with CH_2Cl_2. The first fraction contained the title compound (2.42g, 50%) as a yellow oil with physical properties identical to those above.[165]

(1RS,3RS,1'RS,4'RS)-{Spiro-1,3-dithiolane-2,2'-norborn- 5'-6'-dihydroxy} -1,3-dioxide (215)

Alkene (**206**) (390 mg, 1.81 mmol) was dissolved in water (2 cm^3) and acetone (17 cm^3). To the solution N methylmorpholine N oxide monohydrate (252 mg, 2.16 mmol) and osmium tetroxide ($0.51cm^3$, 0.018 mmol, 0.5 g,/50 cm^3, ^{t}BuOH) were added consecutively and the solution was stirred at room temperature for twenty four hours. Solvents were removed *in vacuo* and the residual water removed by azeotrope with toluene (3 x 40 cm^3). The residue was preabsorbed on silica and subjected to flash chromatography eluting with 10% methanol and 90% methylene chloride. The *title compound* was afforded (351 mg, 77%) as a colourless oil; δ_H (DMSO-d6) 1.36 (1H, dd, J_{gem} 10 and $J_{3'b,4'}$ 3.5 Hz 3'$_b$-H), 1.6 (1H, d, J_{gem} 7.3 and 7'$_b$-H), 1.88 (1H, dd, J_{gem} 10 and $J_{3'a,7'b}$ 1.7 Hz, 3'$_a$-H), 2.05 (1H, d, J_{gem} 7.3, 7'$_a$-H), 2.25 (1H, d, J 2.6 Hz, 4'-H), 2.6 (1H, br s, 1'-H), 3.4-3.6 (4H, m, 4$_{a,b}$ 5$_a$ and 5'-H), 3.85 (1H, m, 5$_b$-H), 4.05 (1H, d, $J_{6',5'}$ 3 Hz, 6'-H), 4.75 (1H, br S, 0H), 5.1 (1H, br S, OH); δ_C 24 (C-7'), 34 (C-3'), 43 (C-1'),46 (C-4'), 48 (C-4), 51 (C-5), 71 (C-5'), 72 (C-6') (C-2) 92;

(1RS,3RS,1'RS,4'RS)-{Spiro-1,3-dithiolane-2,2'-norborn-5',6'-isopropylidinedioxide}-1,3-dioxide (216)

Diol (**215**) (351mg, 1.41mmol) was dissolved in acetone (14 cm^3), tosic acid (2.4 mg, 0.14 mmol and dimethoxypropane (1.7 cm^3, 14.1 mmol) were added and the reaction mixture was stirred at room temperature for three hours. Solvents were removed *in vacuo*, the residue preabsorbed on silica, the residue was subjected to flash chromatography eluting with 10% methanol and 90% methylene choride. The *title compound* was afforded (365mg, 89%) as a white crystalline solid. m.p. 186-188°C (ethyl acetate) (Found C, 49.7; H, 6.31; $C_{12}H_{S2}O_4$ requires C, 49.65; H, 6.21%); υ_{max} ($CHCl_3$)/cm^{-1} 3010, 2980, 1220, 1070, 1050 (S=O); δ_H ($CDCl_3$) 1.3 (3H, s, 8-Me), 1.4 (1H, dd, J_{gem} 15 $J_{3'b,4'}$ 4.5 Hz 3'b-H), 1.48 (1H, s, 8-Me), 1.8 (1H, d, J_{gem} 10.5 Hz, 3a'-H), 2.1 (2H, m, 7'b and 3'b-H), 2.6 (1H, d, *J* 3 Hz, 4'-H), 3.0 (1H, s, 1'-H), 3.3-3.5 (3H, m, 4_b and $5_{a,b}$-H), 4.0(1H, m, 4-H) 4.15 (1H, d, $J_{5,6}$ 5.2 Hz, 5'-H), 4.65 (1H, d, $J_{6,5}$ 5.2 Hz 6'-H); δ_C 22 (C-7'), 24 (2xC-Me), 32 (C-3'), 41 (C-4'), 46 (C-1'), 49 (C-4), 51 (C-5), 80 (C-5'), 81 (C-6'), 93 (C-8'), 110 (C-2); m/z C.I. 290 (M^+ + 1, 100%), 272 (10), 215 (10), 108 (15).

(1'RS,4'RS)Spiro-1,3-dithiolane-2,2'-norborn-5',6'-isopropylidinedioxide (217)

Doixide (**216**) (100 mg, 0.35 mmol) was dissolved in methylene chloride (38 cm^3) and cooled to 0^0C under nitrogen. To the solution, phosphorous tribromide (70 μl, 1.74 mmol) was added *via* syringe and the solution stirred for fifteen minutes. The reaction mixture was poured into water (100 cm^3) and extracted with methylene chloride (3x5 cm^3). The organic extracts were dried ($MgSO_4$) and removed in vacuo to afford the *title compound* (79 mg, 87.4%) as a crystalline solid m.p. 178°C (EtOAc/Pet): δH ($CDCl_3$) 1.3(3H, s, Me), 1.5 (3H, s, Me), 1.6-1.9 (3H, m, 3'a,b and 7'b-H), 2.3 (3H, m, 1',4' and 7'a-H) 3.3 (4H, m, 3a,b,4a,b-H), 4.1 (1H,d,$J_{5',6'}$ 5.5 Hz, 5'-H), 4.6 (1H, d,

$J_{6',5'}$5.5 Hz 6'-H), δC ($CDCl_3$)23, 24, 32, 38.2, 38.7, 39.4, 42, 53, 66, 79, 80, 108; M/z C.I. 259 (M^++1, 100%), 230(20) 201, (20).

(1RS,4RS)Norborn-5',6'-isopropylidinedioxide-2-one (219)

Bissulfide (**217**) (40 mg, 0.15 mmol) was dissolved in methyl iodide (1 cm^3) acetonitrile (2 cm^3) and water (1 cm^3). The solution was stirred at room temperature for forty eight hours after which no disulfide was detected by TLC. The reaction mixture was poured into water (2 cm^3) and extracted with ether (2 x 10 cm^3). The combined organic extract was dried ($MgSO_4$) and solvents were removed *in vacuo*. The residue was preabsorbed on silica and subjected to flash chromatography eluting with 2:1 hexane : ether. The *title compound* was afforded as an oil (11mg, 65%); δ_H ($CDCl_3$) 1.4 (3H, s, CH_3), 1.6 (3H, s, CH_3), 1.7 (2H, m,$7_{a,b}$), 2.05 (2H, m, $3_{a,b}$-H), 2.7 (2H, br s, 1,4-H), 4.39 (1H, br d, *J* 5.25 Hz 5-H), 4.35 (1H, dd, *J* 5.25 and 1.25 Hz, 6-H).

2-oxa-3-oxo-bicyclo-[3.3.0]-oct-5-ene (245)[181]

Norborn-5-ene-2-one (**1**) (500 mg) was dissolved in methylene chloride (50 cm^3) and cooled to 0°C under N_2. To the solution Na_2HPO_4 (1.3 g) was added followed by $(CF_3CO)_2O$ (788 μl) and H_2O_2 (30%, 171 μl, 5.56mmol). After twenty four hours starting material remained, the reaction stopped by the addition of water (20 cm^3) and the aqueous layer was extracted with ethyl acetate (3 x 50 cm^3). The organic extracts were dried ($MgSO_4$) and removed in vacuo to afford an oily residue. The residue was preabsorbed on silica and subjected to flash chromatography eluting with methylene chloride to afford the *title compound* (223 mg) 50% as an oil; δ_H ($CDCl_3$) 2.3 (2H, m, 3_a and 5_a-H), 2.8 (1H, ddd, *J* 11.9, 5.1 and 0.85 Hz 5a-H), 2.85 (1H, dd, *J* 11.9 and *J* 6.5

Hz, 3b-H), 3.18 (1H, m, 4-H), 5.5 (1H, d, *J* 5.1 Hz 8-H), 5.9 (1H, m, 7-H), 6.1 (1H, m, 6-H); m/s 70 ev 123 (M^+-1,5%) 84 (100).

Cis-5-Hydroxyethyl-4-hydroxy-cyclopent-2-enyl (246)

Lactone (**245**) (344 mg, 2.77 mmol) was dissolved in THF (30 cm^3) and cooled to 0°C with stirring under nitrogen. To the cooled solution LAH (137 mg, 3.6 mmol) was added in a single portion. The reaction mixture was stirred for two hours. The reaction was quenched by rapid addition of ethyl acetate (20 cm^3) and the reaction mixture allowed to warm up to room temperature over one hour. The reaction mixture was poured into Na,K- tartrate (30 cm^3) and extracted with ethyl acetate (2 x 30 cm^3). The combined organic extracts were dried ($MgSO_4$) and removed in vacuo to afford the *title compound* (290 mg, 81%) as a colourless oil. The diol (**246**) was acylated without further purification. The *cis* diol (**246**) (290 mg, 2.3) was dissolved in acetic anhydride (10 cm^3) and stirred at room temperature under N_2. To the solution DMAP was stirred for twenty four hours. The solution was poured into water (10 cm^3) and extracted with ethyl acetate (4 x 20 cm^3). Solvents were dried ($MgSO_4$) and removed in vacuo to give a colourless oil. The excess acetic anhydride was removed under high vacuum and the residue subjected to flash chromatography eluting with 1% EtOAc and 99% CH_2Cl_2. *The title compound* (**247**) (229 mg, 47%) was afforded as a colourless oil. δ_H ($CDCl_3$) 1.3 (1H, m, 5-H), 2.6-2.0 (2H, m, 6a,b-H), 2.05 (6H, s, Ac), 2.4 (2H, m, 1-$H_{a,b}$), 4.1 (2H,d *J* 6.75 Hz, 7a,b-H), 5.6 (1H, M, 4-H), 5.9 (1H, m, 2-H), 6.2 (1H, m, 3-H); δ_C 20, 29, 38, 39, 62, 80, 129, 138, 171; m/e 169 (M^+-43 (OAC)) 110 (30), 82 (40), 43 (100).

REFERENCES

REFERENCES

1. O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, 1928, **98**, 460.
2. J. Sauer and R. Sustmann, *Angew. Chem. Int. Ed. Engl.*, 1980, **19**, 779.
3. J.G.Martin and R.K.Hill, *Chem. Rev.*, 1961, **61**, 537.
4. R.A.Y. Jones, "Physical and Mechanistic Organic Chemistry" 2nd Ed., Cambridge University Press, 1984, 352.
5. R.B. Woodward and Hoffmann, *Angew. Chem. Int. Ed. Engl.*, 1969, **8**, 781.
6. For explanation of "Frontier Orbital Theory". I Fleming, "Frontier Orbitals and Organic Chemical Reactions", Wiley, 1976.
7. W. Oppolzer, *Angew. Chem. Int. Ed. Engl.*, 1984, **23**, 876.
8. J.Sauer, *Angew. Chem. Int. Ed. Engl.*, 1967, **6**, 16.
9. M.J.S.Dewar and A.B.Pierini, *J. Am. Chem. Soc.*, 1984,**106**, 203; M.J.S.Dewar, *J. Am. Chem. Soc.*, 1984, **106**, 209.
10. P.D.Bartlett and J.Mallet, *J. Am. Chem. Soc.*, 1976, **98**,143;G.Jenner and J.Rimmelin, *Tetrahedron Lett.*, 1980, **21**, 3039.
11. S.Seltzer, *J. Am. Chem. Soc.*, 1963, **85**, 1360.
12. R. Hiusgen and P. Otto, *Tetrahedron Lett.*, 1968, 4491.
13. S. Ranganathan, D. Nanganathan and A.K. Mehrotra, *Synthesis*, 1977, 289.
14. P.D. Bartlett and B.E. Tate, *J. Am. Chem. Soc.*, 1956, **78**, 2473.
15. J.D.Roberts, E.R.Trinbull, W.Bennett and R.Armstrong, *J. Am. Chem. Soc.*, 1950, **72**, 3116.
16. S. Deakin and T.M. Wibmore, *J.Chem. Soc.*, 1910, **97**, 1971.
17. D.A. Evans, W.L. Scott and L.K. Truesdale, *Tetrahedron Lett.*, 1972, 121.
18. P.S. Wharton and B.T. Aw, *J. Org. Chem.*, 1966, **31**, 3787.
19. C.H. Depuey and P.R. Story, *J. Am. Chem. Soc.*, 1960, **82**, 627.
20. R.M. Nowack, *J. Org. Chem.*, 1963, **28**, 1182.

21. J. Passiuirta and H. Kriger, *Suomen Kemstilehti B.*, 1965, **38**, 182.

22. H. Krieger and S.E Masar, *Suomen Kemstilehti B.*, 1966, **39**, 199.

23. P.K. Freeman, D.M. Ball and D.J. Brown, *J. Org. Chem.*, 1968, **33**, 2211.

24. E.J. Corey, N.M. Weinshenker, T.K.S. Chaaf and W. Huber, *J. Am. Chem. Soc.*, 1969, **91**, 5675.

25. E.J. Corey, U. Koelliker and H. Neuffer, *J. Am. Chem. Soc.*, 1971. **93**, 1489.

26. E.D. Brown, R. Clarkson, T.J. Leeney and G.E. Robinson, *J. Chem. Soc. Chem. Commun.*, 1974, 642; *Ibid*, 1975, 39.

27. J. Ipaktschi, *Chem. Ber.*, 1972, **105**, 1840.

28. H.L. Goering and C.S. Ching, *J. Org. Chem.*, 1975, **40**, 2565.

29. C.L. Stevens and T.H. Coffield, *J. Am. Chem. Soc.*, 1951, **73**, 103.

30. E. Vieira and P. Vogel, *Helv. Chim. Acta.*, 1982, **65**, 1700.

31. E.J. Corey, S. Ravindanathan, S. Terashima, *J. Am. Chem. Soc.*, 1971, **93**, 4326.

32. C.S. Marvel, J. Dec, H.G. Cooke and J. Cowan, *J. Am. Chem. Soc.*, 1940, **62**, 3495.

33. J.E. McMurry, and J. Melton, *J. Org. Chem.*, 1973, **38**, 4367.

34. S. Ranganathan, D. Ranganathan and A.K. Mehrota, *J. Am. Chem. Soc.*, 1974, **96**, 5261.

35. S. Ranganathan,D. Ranganathan and R. Iyengar, *Tetrahedron*, 1976, **32**, 961.

36. B.M. Trost and Y. Tamaru, *J. Am. Chem. Soc.*, 1975, **97**, 3528.

37. H.H. Wasserman and B.H. Lipshutz, *Tetrahedron Lett.*, 1975, **16**, 4611.

38. T.R. Darling and C.S. Foote, *J. Am. Chem. Soc.*, 1974, **96**, 1625.

39. L. Stella, and J. Boucher, *Tetrahedron*, 1985, **41**, 875.

40. S.C. Temin, *J. Org. Chem.*, 1957, **22**, 1714.

41. B.M. Trost, D. O'Kronghy and J. L'Belletire, *J. Am. Chem. Soc.*, 1980, **102**, 7595; T. Mukaiyama and N. Iwasawa, *Chem. Lett.*, 1981, 29.

42. S. Hashimoto, N. Kemenshima and K. Koga, *J.Chem. Soc. Chem. Commun.*, 1979, 437.

43. W. Oppolzer, C. Chapuis, G.M. Dao, D. Reichlin and T. Godel, *Tetrahedron Lett.*, 1982, **23**, 4781.

44. F. Farmer and J. Hamer, *J. Org. Chem.*, 1966, **31**, 2418; J. Sauer and J. Kredel, *Tetrahedron Lett.*, 1966, **7**, 6359.

45. H.M. Walborsky, L. Barash and T.C. Davis, *Tetrahedron,* 1963, **19**, 2333.

46. T.Suga, K.Imamura and T.Shishibori, J.*Chem. Soc., Chem Commun.*, 1971, 126

47. H.O. House, "Modern Synthetic Reactions". 2nd ed, W.A. Benjamin, Califonia, 1972, p.150.

48. E.J. Corey and H.E. Ensley, *J. Am. Chem. Soc.*, 1975,**97**, 6908.

49. D.S. Watt and S.J. Selikson, *J. Org. Chem.*, 1975, **40**, 267; H. Wasserman and B.H. Lipshutz, *Tetrahedron Lett.*, 1975, **16**, 1731.

50. W. Oppolzer, M. Kurth, D. Reichlin and F. Moffat, *Tetrahedron Lett.*, 1981, **22**, 2545.

51. C. Le Drain and A. Greene, *J. Am. Chem. Soc.*, 1982, **104**, 5473.

52. W. Oppolzer, M. Kurth, D. Reichlin, C. Chapuis, M. Mohnhaupt and F. Moffat, *Helv. Chim. Acta.*, 1981, **64**, 2802.

53. J. A. Dale, D.L. Dull and H.S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.

54. W. Oppolzer, C. Chapuis, C.M. Dao, D. Reichlin and T. Godel, *Tetrahedron Lett.*, 1982, **23**, 4781.

55. W. Oppolzer, C. Robbiani and K. Battig, *Helv. Chim. Acta.,* 1980, **63**, 2015.

56. R.J. Loncharich, T.R. Schwartz and K.N. Houk, *J. Am. Chem. Soc.*, 1987, **109**, 14.

57. W. Oppolzer and C. Chapuis, *Tetrahedron Lett.*, 1984, **25**, 5383.

58. W. Oppolzer, C. Chapuis and G. Bernardinelli, *Tetrahedron Lett.*, 1984, **25**, 5885.

59. W. Oppolzer, M.J. Kelly and G. Bernardinelli, *Tetrahedron Lett.*, 1984, **25**, 5889.

60. U. Prelog, *Helv. Chim. Acta.*, 1953, **36**, 308; U. Prelog and G. Tsatas, *Helv. Chim. Acta.*, 1953, **36**, 1178.

61. K.N. Houk and R.W. Strozier, *J. Am. Chem. Soc.*, 1973, **95**, 4092; K.N. Houk and R.W. Strozier, *J. Am. Chem. Soc.*, 1973, **95**, 4094.

62. P.A. Carrupt and P. Vogel, *Tetrahedron Lett.*, 1979, **20**, 4533.

63. W.L. Nelson, D.R. Allen and F.F. Vinerizi, *J. Med. Chem.*, 1971, **14**, 698; H. Katuski and H. Nishizawa, *Heterocycles*, 1981, **16**, 1287.

64. A. Murai, K. Takahashi, H. Takestura, T. Masamune, *J. Chem. Soc., Chem. Commun.*, 1981, 221.

65. T.A. Eggeltta, H. deKonig and H.O. Huisman, *J. Chem. Soc., Perkin Trans. I.*, 1978, 980.

66. P.A. Grieco, R.E. Zelle, R. Lis and J. Finn, *J. Am. Chem. Soc.*, 1983, **105**, 1403.

67. H. Kotsuki, H. Nishizawa, M. Ochi and K. Mastuoka, *Bull. Chem. Soc. Jpn.*, 1982,**55**, 496; W.G. Dauben and H.O. Krabbeuhott, *J. Am. Chem. Soc.*, 1976, **98**, 1992; J. Rimmelin, G. Jenner and P. Rimmelin, *Bull. Soc. Chin. Fr. II*, 1978, 461.

68. A.W. McCulloch, D.G. Smith and A.G. McInnes, *Can. J. Chem.*, 1974, **52**, 1013; E. Vieira, and P. Vogel, *Helv. Chim. Acta*, 1982, **65**, 1700.

69. E. Vieira and P. Vogel, *Helv. Chim. Acta.*, 1983, **66**, 1865.

70. A. Oku and S. Arita, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 3337.

71. J. Wagner, E. Vieira and P. Vogel, *Helv. Chim. Acta*, 1988, **71**, 624.

72. Y. Auberson and P. Vogel, *Helv. Chim. Acta.*, 1989, **72**, 278.

73. R. M. Bimwala and P. Vogel, *Helv. Chim. Acta.*, 1989, **72**, 1825.

74. F. Gasparini and P. Vogel, *Helv. Chim. Acta.*, 1989, **72**, 271.

75. D. Fattori, E. deGuchteneere and P. Vogel, *Tetrahedron Lett.*, 1989, **30**, 7415.

76. J-L Reymond and P. Vogel, *Tetrahedron Asymmetry*, 1990, **1**, 729.

77. J-L. Reymond and P. Vogel, *J.*Chem. *S*oc., *Chem. Commun.*, 1990, 1070.

78. G.H. Posner, "The Chemistry of Sulfones and Sulfoxides", Ed. S. Patai, Z. Rappoport and C. Stirling, John Wiley and Sons, New York, 1988, Chapter 16, page 845 and references cited therein.

79. O. DeLucchi and L. Pasquato, *Tetrahedron*, 1988, **44**, 6755.

80. C. Maignan, R.A. Raphael, *Tetrahedron*, 1983, **39**, 3245.

81. J.E. Mulvaney and R.A. Ottavicini, *J. Polymer Sci.*, 1970, **8**, 2293.

82. R. Tanikaga, Y. Yabuki, N. Ono and A. Kaji, *Tetrahedron Lett.*, 1976, **17**, 2257.

83. P. Bakuzis, M.L.F. Bakuzis, C.C. Fortes and R. Santos, *J. Org. Chem.*, 1976, **41**, 2769.

84. D.W. Chasar and T.M. Pratt, *Synthesis*, 1976, 262.

85. M.A. Brimble and B.R. Davis, *Tetrahedron*, 1985, **41**, 4965.

86. Y. Arai, S., Kuwayama, Y. Takeuch and T. Koizumi, *Tetrahedron Lett.*, 1985, **26**, 6205.

87. T. Koizumi, I. Hakamada and E. Yoshii, *Tetrahedron Lett.*, 1984, **25** 87.

88. L.A. Paquette, R.E. Moreck, B. Harirchian and P. Magnus, *J. Am. Chem. Soc.*, 1978, **100**, 1597.

89. R. V. Williams and X. Lin, *J.Chem Soc,. Chem. Commun.*, 1989, 1872.

90. I. Fleming and A. Pearce, *J.Chem Soc., Chem Commun.*, 1975, 633.

91. F. Cooke, R. Moerck, J. Schwindeman and P. Magnus, *J. Org. Chem.*, 1980, **45**, 1046.

92. A.G. Brook and D.G. Anderson, *Can. J. Chem.*, 1968, **46**, 2115.

93 A. G. Brook, D.M. MacRae and W. W. Limburg, *J. Am. Chem. Soc.*, 1967, **89**, 5493.

94. C. Maignan and F. Belkasmioui, *Tetrahedron Lett.*, 1988, **29**, 2823.

95. C. Maignan, A. Guessous and F. Rouessac, *Bull. Soc. Chim. France*, 1986, 645.

96. G.A. Olah, A. Huisgen, B.P. Sing and A.K. Mehrotra, *J. Org. Chem.*, 1983, **48**, 3667.

97. Y. Arai, S. Kuwayama, Y. Takeuchi, and T. Koizumi, *Synth. Commun.*, 1986, **16**, 233.

98. M. Mikolajczyk, W. Midura, S. Grzejszczak, A. Zatorski and A. Chefczynska, *J. Org. Chem.*, 1978, **43**, 473.

99. J. K. Whitesell, *Chem. Rev.*, 1989, **89**, 1581.

100. J. E. Richman, J.L. Herman and R.H. Schlessinger, *Tetrahedron Lett.*, 1973, 3267.

101. Reaction with Danifshefsky's diene is reported, ref 15 of ref 97. Reference reports that the reaction had been performed but gave no futher reference.

102. $ZnCl_2$ was reported to increase selectivity, ref 16 of ref 97. Reference stated reactions performed with this Lewis acid showed enhanced selectivity but gave no futher reference or selectivity obtained.

103. O. DeLucchi, D. Fabbri and V. Lucchini, *Synlett*, 1991, 565.

104. R. Lopez, J.C. Carretero, *Tetrahedron Asymmetry*, 1991, **2**, 93.

105. B.M. Trost, T.N. Saltzmann and K.Hiroi, *J. Am. Chem. Soc.*, 1976, **98**, 4887; G.H. Posner, J.P. Mallamo, M. Hulce and L.L. Frye, *J. Am. Chem. Soc.*, 1982, **104**, 4180.

106. Example of Anderson reaction : R. Annunziata, M. Cinquini and F. Cozzi, *Synthesis*, 1979, 535 and ref therein.

107. S.D. Kahn and W.J. Hehre, *Tetrahedron Lett.*, 1986, **27**, 6041.

108. T. Koizumi, Y. Arai and H. Takayama, *Tetrahedron Lett.*, 1987, **28**, 3689.

109. For review : D. Seebach, R. Imwinkerlied and T. Weber,"Modern Synthetic Methods", Ed., R. Scheffold, Springer Verlag : Berlin, 1986, **4**, 125; D. Seebach, R. Naef, G. Calderari, *Tetrahedron*, 1984, **40**, 1313.

110. J. Mattay, J. Mertes and G. Maas, *Chem. Ber*, 1989, **122**, 327.

111. W.R. Roush, A.P. Essenfeld, J.S. Warmus and B.B. Brown, *Tetrahedron Lett.*, 1989, **30**, 7305.

112. J. Zimmerman and D. Seebach, *Helv. Chim. Acta.*, 1987, **70**, 1104 .

113. W.R. Roush and B.B. Brown, *Tetrahedron Lett.*, 1989, **30**, 7309.

114. J. Nakayama, K. Fujiwara and Masamatsu Hosino, *Bull. Chim. Soc,, Jpn.*, 1976, **49**, 3567.

115. J. Nakayama, K. Fujiwara and M. Hosino, *Chem. Lett.*, 1975, 1099.

116. J. Nakayama, *Synthesis*, 1975, 168; J. Nakayama, *J.Chem.Soc., Chem. Commun.*, 1974, 166.

117. For review articles see: J. Nakayama, *Sulfur Reports*, 1985, **4**, 159.

118. E. Keller and R.G. Hayes, *J. Phys. Chem.*, 1969, **73**, 3901.

119. J. Nakayama, E. Seki and M. Hoshini, *J.Chem.Soc., Perkin Trans I.*, 1978, 468; K. Akiba, K. Ishikawa and N. Inamoto, *Bull. Chem. Soc. Jpn.*, 1978, **351**, 2674.

120. J. W. Patterson and J.E. McMurry, *J. Chem. Soc., Chem. Commun.*, 1971, 488.

121. G.J.S. Doad, *J. Chem. Research (S).*, 1987, 370.

122. K. Ishikawa, K. Akiba and N. Inamoto, *Tetrahedron Lett.*, 1976, **17**, 3695; H. Gros and B. Costisella, *Synthesis*, 1977, 622.

123. D. Wallis, *Chem. Ind.*, 1958, 1568

124. S.D. McCathy, Unpublished results, 1991.

125. R.C. Ebersole and F.C. Chang, *J. Org. Chem.*, 1973, **38**, 2713.

126. V.K. Aggarwal, I.W. Davies, J. Maddock, M.F. Mahon and K.C. Malloy, *Tetrahedron Lett.*, 1990, **31**, 1990

127. J.A. Marshall, *Synth. Commun.*, 1986, **16**, 1953.

128. K.B. Sharpless, R.F. Lauer and A.Y. Teranishi, *J. Am. Chem. Soc.*, 1973, **95**, 6137; H.J. Reich, I. L. Reich, J. Renga, *J. Am. Chem. Soc.*, 1973, **95**, 5813; A.J. Beckwith and P.E. Pigou, *Aust. J. Chem.*, 1986, **39**, 77; P.P. Davis, J.S. Grossert, R.F. Langler and W.S. Mantle, *Org. Mass. Spec.*, 1977, **12**, 659.

129. J.L. Roberts, P.S. Borromeo and C.D. Poulter, 1977, **19**, 1621; *ibid*, 1977, **15**, 1299; S. Danishefsky, P.F. Schuda, T. Kitahara and S.J. Etheredge, *J. Am. Chem. Soc.*, 1977,**99**, 6066.

130. P.A. Grieco, *Synthesis*, 1975, 67.

131. J.C. Jaszberenyi, I. Petrikovics, E.J. Gunda and S. Hoszjafi, *Acta Chim. Acad. Sci.*, 1982, **110**, 81; Tramontini and L. Angiolini, *Tetrahedron*, 1990, **46**, 1791; A.P. Beracieta and D.A. Whiting, *J.Chem. Soc., Perkin Trans I.*, 1978, 1257.

132. V.K. Aggarwal, I.W. Davies, R.J. Franklin, J. Maddock, M.F. Mahon and K.C. Malloy, *J.Chem.Soc., Perkin Trans., 1,* 1991, 662.

133. O. Samuel, B. Ronan and H.B. Kagan, *J. Org. Met. Chem.*, 1989, **43**, 370.

134. P.C. Bulman-Page and E.S. Namwindwa, *Synlett,* 1991, 80.

135. V.K. Aggarwal and E. Moya, *J. Org. Chem.*,1992, **57** 1107.

136. W.H. Parsons, R.H. Schlessinger and M.L. Quesada, *J. Am. Chem. Soc.*, 1980, **102**, 7583; J. Malek and M. Cerny, *Synthesis*, 1972, 217.

137. R.A. Bell and J.V. Turner, *Tetrahedron Lett.*, 1981, **22**, 4872.

138. J.K. Gainnonski and H.M. Walborsky, *J. Org. Chem.*, 1986, **51**, 2863.

139. H.C. Brown, S. Narasimhan and Y.M. Choi, *J. Org. Chem.*, 1982, **47**, 4702.

140. H.C. Brown, *Tetrahedron Lett.*, 1987, **28**, 5161.

141. K. Soati and A. Ookawa, *J. Org. Chem.* 1986, **51**, 4000.

142. D.J.Peterson, *J. Org Chem.*, 1968, **33**, 780; T. Cohen, *J. Am. Chem. Soc.*, 1984, **106**, 3245.

143. H. Ogura, O. Sato and K. Takeda, *Tetrahedron Lett.*, 1981, **22**, 4817.

144. R.B. Miller and R.D. Nash, *Tetrahedron*, 1974, **30**, 2961.

145. E.E. Van-Tamelen and S.R. Bach, *J. Am. Chem. Soc.*, 1955, **75**, 4683.

146. M. Madesclaire, *Tetrahedron*, 1988, **44**, 6537.

147. D.L. Hughes, *J. Am. Chem. Soc.*, 1988, **110**, 6487.

148. V.K. Aggarwal, R.J. Franklin and M.J. Rice, *Tetrahedron Lett.*, 1991, **32**, 7743.

149. L.F.Fieser and M. Fieser, "*Reagents for Organic Synthesis*", Wiley, New York 1986, **12**, 232.

150. N.L. Yang and L. Rodriguez, *Synlett*, 1990, 227.

151. M. Schlosser, T.Jenny and Y. Guggisburg, *Synlett*, 1990, 704.

152. M.E. Jung, *Synlett.*, 1990, 186.

153. J.F. Blake and W.L. Jorgensen, *J. Am. Chem. Soc.*, 1991, **113**, 7430.

154. Breslow and U. Maitra, *Tetrahedron Lett.*, 1984, **25**, 1239

155. A. Ben-Naima, "Hydrophobic Interactions", Plenum Press, New York, 1980.

156. D.C. Rideout and R. Breslow, *J. Am. Chem. Soc.*, 1980, **102**, 7816.

157. J.R. McCabe, *Acc. Chem. Res.*, 1974, **7**, 251.

158. R. Gompper, *Angew. Chem. Int. Ed. Engl.*, 1968, **8**, 312.

159. D.M. Birney and K.N. Houk, *J. Am. Chem. Soc.*, 1990, **112**, 4127.

160. A. Waldner, A. De Mesmaeker, P. Hoffman, T. Mindt and T. Winkler, *Synlett*, 1991, 101.

161. J.K. Snyder, *J. Am. Chem. Soc.*, 1989, **111**, 1523.

162. R. Breslow, *Acc. Chem. Res.*, 1991, **24**, 159; R. Breslow, U. Maitra and D. Rideout, *Tetrahedron Lett.*, 1988, **24**, 1901; R. Breslow and U. Maitra,

Tetrahedron Lett., 1984, **25**, 1239

163. P.A. Grieco, K. Yoshida and P. Garner, *J. Org. Chem*, 1983, **48**, 3139,; K. Yoshida and P.A. Grieco, *J. Org. Chem.*, 1984, **49**, 5257; P.A. Grieco, J.J. Nunes and M.D. Gaul, *J. Am. Chem. Soc.*, 1990, **112**, 4595; P.A. Grieco and S.D. Larsen, *J. Am. Chem. Soc.*, 1985, **107**, 1768; P.A. Grieco, P. Garner and Z. He, *Tetrahedron Lett.*, 1983, **24**, 1897.

164. P.H. Von Hippel and T. Schleich, *Acc. Chem. Res.*, 1969, **2**, 257.

165 A. Waldner, *Tetrahedron Lett.*, 1989, **30**, 3061.

166. P.R. Heaton, J.M. Midgley and W.B. Whalley, *J.Chem.Soc., Perkin Trans. I.*, 1978, 1011.

167. N. Katagiri, S. Ise, N. Watanabe and C. Kaneko, *Chem. Pharm. Bull*, 1990, **38**, 3242.

168. B.T. Grovel and D. Seebach, *Synthesis*, 1977, 357.

169. D. Barton, *J.Chem. Soc., Chem. Commun.*, 1970, 1683; O. Barton, *J.*Am. Chem. Soc., 1970, 35, 2430.

170. P. Vogel, *Tetrahedron*, 1990, **45**, 7019.

171. F. Barré-Sinoussi, J.C. Chermann, F-Rey, M.T. Nugeyre, S. Chamaret, T. Gruest, C. Dauguet, L. Axler-Blin, F. Bezinet-Brun, C. Rouzioux, W. Rozenbaum, L. Motagner, *Science*, 1983, **220**, 868. (b) J.A. Levy, A.D. Hoffman, S.M. Kramer, J.A. Landis, J.M. Shimabakuro, L.S. Oshiro, *Science*, 1984, **225**, 840.

172. J. Ayala and J.A. Kiger "Modern Genetics", World Student Series 2nd ed Page 90 and 394.

173. C.A. Fletcher, H. Hilpert, P.L. Myers, S.M. Roberts and R. Storer, *J. Chem. Soc., Chem. Commun.*, 1989, 1707; R.M. Highcock, H. Hilpert, P.. Myers, S.M. Roberts and R. Storer, *J. Chem. Soc., Perkin Trans 1*, 1991, 1127.

174. S.M. Roberts, *Chem in Britain*, 1991, 518.

175. H. Mitsuya, K.J. Weinhold, P.A. Furman, M.H. St. Clair, S. Nasinott-Lehrman, R.C. Gallo, D. Bolognesi, D.W. Barry and S. Broder, *Proc. Natl. Acad. Sci.* USA, 1985, **82**, 7096.

176. R. Vince and M. Hua, *J. Med. Chem.*, 1990, **33**, 17.

177. S.J.C. Taylor, A.G. Sutherland, C. Lee, R. Wisdom, S. Thomas, S.M. Roberts and C. Evans, *J. Chem. Soc., Chem. Commun.*, 1990, 1120.

178. E.A. Saville-Stones, S.D. Lindell, N.S. Jennings, J.C. Head and M.J. Ford, *J. Chem. Soc., Perkin Trans.* 1, 1991, 2603.

179. B. Trost, *J. Am. Chem. Soc.*, 1976, **98**, 8516 (b) B. Trost, *J. Org. Chem.*, 1979, **44**, 3451.

180. S.A. Benner, *Tetrahedron Lett.*, 1991, **32**, 7029.

181. G.R.Krow, *Tetrahedron*, 1981, **76**, 2697.

182 K.Sakai, *Chem., Lett.*,1986, 353.

183. D.D. Perrin, W.L.F. Armarego and D.R. Perrin, Purification of laboratory chemicals, Pergamon, Oxford, 1980, 2nd, Ed.

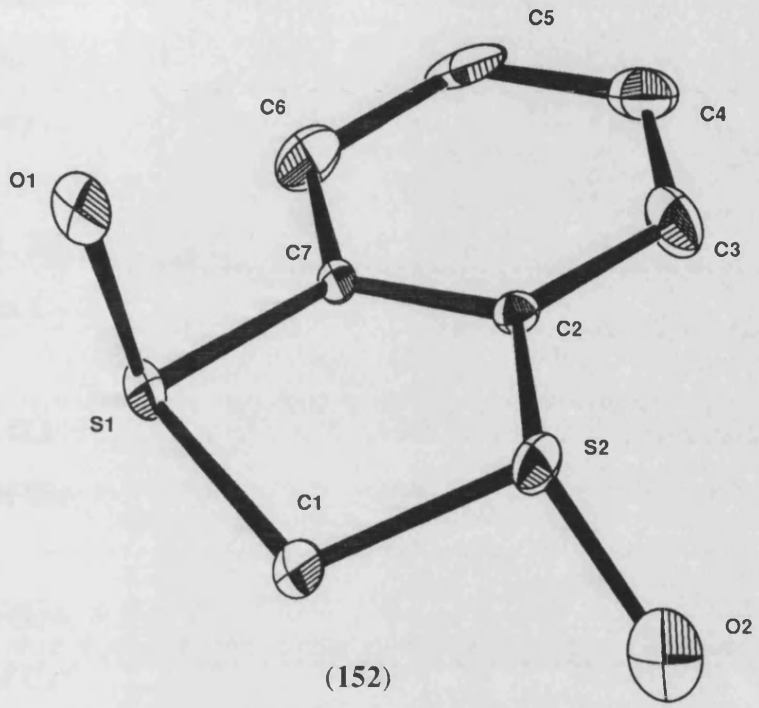
184. V. VanRheesen, R.C.Kelly and D.Y. Cha, *Tetrahedron Lett.*, 1976, **23**, 1973

185. W. C. Still, M. Kahn, A. Mitra, *J.Org. Chem.*, 1978, **43**, 2923

APPENDIX ONE

CRYSTAL DATA

NOTE ON (152).



(**152**)

A crystal of approximate dimensions 0.2 x 0.2 x 0.3 mm was used for data collection. ***Crystal data:*** $C_7H_6O_2S_2$, M = 120.1, triclinic, a = 6.826(1), b = 8.344(1), c = 10.962(2)Å, α = 110.41(1), β = 89.01(2), γ = 102.55(2)°, U = 570.02 Å^3, space group $P1$, Z = 2, D_c = 1.58 gcm^{-3}, μ(Mo-K_α) = 3.9 cm^{-1}, $F(000)$ = 256. Data were measured at room temperature on a Hilger and Watts Y290 four-circle diffractometer in the range $2 \leq \theta \leq 24^\circ$. 1932 reflections were collected of which 891 were unique and observed with $I \geq 3\sigma(I)$. Data were corrected for Lorentz and polarization effects and also for absorption[1]. The structure was solved by Direct methods and refined using the SHELX[2,3] suite of programs. In the final stages of convergence all atoms were treated anisotropically. Hydrogen atoms were included at calculated positions.

Final residuals after 10 cycles of full-matrix least squares refinement were $R = R_w$ = 0.0735 for unit weights. The total number of parameters varied was 136. Max. final

shift/esd was 0.003, the average being 0.001. The max. and min. residual densities were 0.25 and -0.21 $eÅ^{-3}$ respectively. Final fractional atomic coordinates and isotropic thermal parameters, bond distances and angles are given in the following tables. Tables of anisotropic temperature factors and hydrogen atom positions are available as supplementary data.

1. Walker N., Stuart D., DIFABS, a program to correct for absorption effects in crystals, Acta Cryst., (1983),A39,158.

2. Sheldrick G.M., SHELX86, a computer program for crystal structure determination, University of Göttingen, 1986.

3. Sheldrick G.M., SHELX76, a computer program for crystal structure determination, University of Cambridge, 1976.

TABLE 1 Fractional atomic coordinates and thermal parameters (Å) for **(152)**

Atom	x	y	z	Uiso or Ueq (***)
S1	0.25650(4)	0.38674(3)	0.48749(2)	0.0267(1) ***
S2	0.29281(3)	0.50294(3)	0.26420(2)	0.0217(1) ***
O1	0.13954(11)	0.25504(11)	0.51830(7)	0.0455(5) ***
O2	0.38138(10)	0.65845(8)	0.28917(6)	0.0309(4) ***
C1	0.43324(12)	0.30420(11)	0.42282(8)	0.0178(5) ***
C2	0.55761(15)	0.19483(13)	0.47527(10)	0.0339(6) ***
C3	0.69980(15)	0.14482(14)	0.41996(12)	0.0408(7) ***
C4	0.71221(15)	0.19280(15)	0.31975(12)	0.0461(8) ***
C5	0.58792(15)	0.30085(13)	0.26669(9)	0.0345(6) ***
C6	0.45023(12)	0.35257(11)	0.32044(7)	0.0157(5) ***
C7	0.14155(13)	0.45894(12)	0.36041(8)	0.0236(5) ***

TABLE 2 Fractional atomic coordinates for the hydrogen atoms

Atom	x	y	z
H2	0.5432	0.1504	0.5540
H3	0.8012	0.0647	0.4590
H4	0.8214	0.1485	0.2793
H5	0.5992	0.3412	0.1866
H71	0.0679	0.5654	0.3749
H72	0.0471	0.3690	0.3270

TABLE 3 Anisotropic thermal parameters (Å)

Atom	U11	U22	U33	U23	U13	U12
S1	0.028(1)	0.030(1)	0.022(1)	-0.002(1)	0.010(1)	0.003(1)
S2	0.024(1)	0.022(1)	0.019(1)	0.005(1)	0.000(1)	0.000(1)
O1	0.038(5)	0.047(5)	0.051(5)	0.024(4)	0.022(4)	-0.001(4)
O2	0.031(4)	0.014(4)	0.048(5)	0.021(3)	0.001(3)	0.005(3)
C1	0.013(5)	0.014(5)	0.026(5)	-0.001(4)	0.003(4)	0.003(4)
C2	0.034(6)	0.027(6)	0.042(7)	0.009(5)	-0.003(5)	0.001(5)
C3	0.023(6)	0.025(6)	0.075(10)	0.000(6)	-0.005(6)	0.012(5)
C4	0.019(6)	0.034(7)	0.085(10)	-0.017(7)	0.021(6)	-0.001(5)
C5	0.037(6)	0.025(6)	0.042(7)	-0.009(5)	0.017(5)	-0.005(5)
C6	0.017(5)	0.012(5)	0.019(5)	-0.007(4)	0.000(4)	0.000(4)
C7	0.021(5)	0.017(5)	0.033(6)	0.002(4)	0.008(4)	0.001(4)

TABLE 4 Bond lengths (Å)

S1 -O1	1.493(8)	S1 -C1	1.777(9)
S1 -C7	1.817(10)	S2 -O2	1.482(8)
S2 -C6	1.804(9)	S2 -C7	1.799(10)
C1 -C2	1.406(14)	C1 -C6	1.376(13)
C2 -C3	1.406(17)	C3 -C4	1.342(19)
C4 -C5	1.402(18)	C5 -C6	1.371(14)

TABLE 5 Bond angles ( )

C1	-S1	-O1	108.6(5)	C7	-S1	-O1	105.0(5)
C7	-S1	-C1	90.9(4)	C6	-S2	-O2	107.0(4)
C7	-S2	-O2	109.8(5)	C7	-S2	-C6	91.1(4)
C2	-C1	-S1	121.3(8)	C6	-C1	-S1	118.7(7)
C6	-C1	-C2	119.9(9)	C3	-C2	-C1	117(1)
C4	-C3	-C2	122(1)	C5	-C4	-C3	121(1)
C6	-C5	-C4	117(1)	C1	-C6	-S2	116.2(7)
C5	-C6	-S2	121.1(8)	C5	-C6	-C1	122.5(9)
S2	-C7	-S1	113.7(5)				

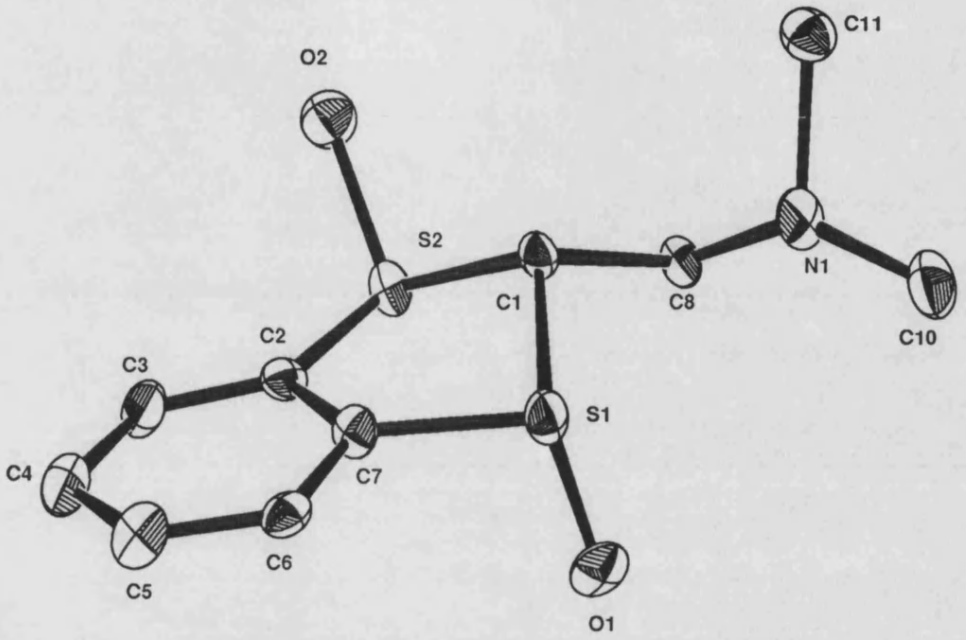
TABLE 6 Intermolecular distances (Å)

O1	...H3	2.99	1	1.0	0.0	0.0
O1	...H3	2.74	-1	1.0	0.0	1.0
O1	...H71	2.65	-1	0.0	1.0	1.0
O1	...H5	2.33	-2	1.0	1.0	0.0
O2	...H2	2.56	-1	1.0	1.0	1.0
O2	...H4	2.48	2	1.0	-1.0	0.0
O2	...H72	2.41	2	0.0	-1.0	0.0
C4	...H72	2.89	1	-1.0	0.0	0.0
C5	...H71	2.81	2	0.0	0.0	0.0

TABLE 7 Intramolecular distances (Å)

S1	...C2	2.78	S1	...H2	2.95
S1	...C6	2.72	S1	...H71	2.39
S1	...H72	2.39	S2	...C1	2.71
S2	...C5	2.77	S2	...H5	2.93
S2	...H71	2.37	S2	...H72	2.37
O1	...C1	2.66	O1	...C7	2.63
O1	...H72	2.60	O2	...C6	2.65
O2	...C7	2.69	O2	...H71	2.81
C1	...H2	2.17	C1	...C3	2.40
C1	...C4	2.75	C1	...C5	2.41
C1	...C7	2.56	C2	...H3	2.15
C2	...C4	2.40	C2	...C5	2.82
C2	...C6	2.41	H2	...C3	2.18
C3	...H4	2.10	C3	...C5	2.39
C3	...C6	2.73	H3	...C4	2.09
C4	...H5	2.17	C4	...C6	2.37
H4	...C5	2.15	H5	...C6	2.14
C6	...C7	2.57			

NOTE ON (172).



(172)

A crystal of approximate dimensions 0.2 x 0.2 x 0.3 mm was used for data collection. ***Crystal data:*** $C_{10}H_{13}O_2NS_2$, M = 120.1, triclinic, a = 6.826(1), b = 8.344(1), c = 10.962(2)Å, $\underline{\alpha}$ = 110.41(1), $\underline{\beta}$ = 89.01(2), $\underline{\gamma}$ = 102.55(2)°, U = 570.02 Å^3, space group $P1$, Z = 2, D_c = 1.58 gcm^{-3}, μ(Mo-K_α) = 3.9 cm^{-1}, F(000) = 256. Data were measured at room temperature on a Hilger and Watts Y290 four-circle diffractometer in the range $2 \leq \theta \leq 24^\circ$. 1932 reflections were collected of which 891 were unique and observed with $I \geq 3\sigma(I)$. Data were corrected for Lorentz and polarization effects and also for absorption[1]. The structure was solved by Direct methods and refined using the SHELX[2,3] suite of programs. In the final stages of convergence all atoms were treated anisotropically. Hydrogen atoms were included at calculated positions.

Final residuals after 10 cycles of full-matrix least squares refinement were $R = R_w$ =

0.0735 for unit weights. The total number of parameters varied was 136. Max. final shift/esd was 0.003, the average being 0.001. The max. and min. residual densities were 0.25 and -0.21 $eÅ^{-3}$ respectively. Final fractional atomic coordinates and isotropic thermal parameters, bond distances and angles are given in the following tables. Tables of anisotropic temperature factors and hydrogen atom positions are available as supplementary data.

1. Walker N., Stuart D., DIFABS, a program to correct for absorption effects in crystals, Acta Cryst., (1983),A39,158.

2. Sheldrick G.M., SHELX86, a computer program for crystal structure determination, University of Göttingen, 1986.

3. Sheldrick G.M., SHELX76, a computer program for crystal structure determination, University of Cambridge, 1976.

TABLE 1 Fractional atomic coordinates and thermal parameters (Å) for (**172**)

Atom	x	y	z	Uiso or Ueq (***)
S1	0.4385(6)	-0.0062(4)	0.6631(3)	0.039(2) ***
S2	0.2650(6)	-0.2355(4)	0.8165(3)	0.040(2) ***
O1	0.2795(16)	-0.0843(12)	0.5559(8)	0.051(7) ***
O2	0.3152(18)	-0.2185(12)	0.9543(8)	0.059(7) ***
N1	0.1668(20)	0.2349(13)	0.8305(10)	0.051(8) ***
C1	0.3232(19)	-0.0129(14)	0.8137(11)	0.030(8) ***
C2	0.5672(22)	-0.1773(15)	0.6582(12)	0.036(8) ***
C3	0.7170(22)	-0.2150(16)	0.5774(12)	0.038(9) ***
C4	0.7929(25)	-0.3597(19)	0.5690(14)	0.051(10) ***
C5	0.7042(23)	-0.4749(17)	0.6338(13)	0.046(10) ***
C6	0.5409(24)	-0.4362(17)	0.7105(13)	0.045(10) ***
C7	0.4780(23)	-0.2885(14)	0.7250(11)	0.038(8) ***
C8	0.1232(19)	0.0523(14)	0.8190(12)	0.029(8) ***
C9	0.0007(27)	0.2809(18)	0.7841(14)	0.058(11) ***
C10	0.2358(25)	0.3509(16)	0.9674(12)	0.048(10) ***

TABLE 2 Fractional atomic coordinates for the hydrogen atoms

Atom	x	y	z
H11	0.4230	0.0708	0.8977
H31	0.7745	-0.1347	0.5202
H41	0.9240	-0.3833	0.5151
H51	0.7556	-0.5928	0.6216

H61	0.4760	-0.5216	0.7625
H81	0.0484	0.0392	0.9038
H82	0.0267	-0.0263	0.7323
H91	-0.0444	0.1935	0.6851
H92	0.0465	0.4143	0.7863
H93	-0.1241	0.2705	0.8448
H101	0.3597	0.3099	0.9985
H102	0.1141	0.3414	1.0306
H103	0.2847	0.4852	0.9721

TABLE 3 Anisotropic thermal parameters (Å)

Atom	U11	U22	U33	U23	U13	U12
S1	0.044(3)	0.037(2)	0.036(2)	0.016(1)	0.010(2)	0.017(2)
S2	0.050(3)	0.029(2)	0.042(2)	0.014(1)	0.002(2)	0.009(2)
O1	0.064(9)	0.062(6)	0.029(5)	0.012(4)	0.012(5)	0.030(5)
O2	0.089(10)	0.052(6)	0.035(5)	0.023(4)	0.010(5)	0.021(5)
N1	0.079(12)	0.033(6)	0.041(6)	0.017(5)	0.020(6)	0.027(6)
C1	0.026(10)	0.032(6)	0.031(6)	0.013(5)	0.003(6)	0.005(5)
C2	0.033(11)	0.039(7)	0.038(7)	0.008(6)	0.004(6)	0.014(6)
C3	0.034(12)	0.047(8)	0.032(7)	0.005(6)	-0.013(6)	0.008(7)
C4	0.038(12)	0.061(9)	0.055(9)	0.006(7)	0.002(7)	0.030(8)
C5	0.043(12)	0.043(8)	0.053(9)	0.006(7)	-0.007(7)	0.023(7)
C6	0.047(13)	0.045(8)	0.044(8)	0.014(6)	-0.007(7)	0.019(7)
C7	0.069(12)	0.018(6)	0.025(6)	0.003(5)	-0.007(6)	0.006(6)
C8	0.017(10)	0.029(6)	0.041(7)	0.006(5)	-0.006(6)	0.000(5)
C9	0.072(14)	0.041(8)	0.060(9)	0.023(7)	0.008(8)	0.019(8)
C10	0.067(14)	0.033(7)	0.043(8)	0.003(6)	-0.008(7)	0.006(7)

TABLE 4 Bond lengths (Å)

S1 -O1	1.478(10)	S1 -C1	1.829(11)
S1 -C2	1.817(13)	S2 -O2	1.506(9)
S2 -C1	1.824(11)	S2 -C7	1.799(15)
N1 -C8	1.447(14)	N1 -C9	1.428(19)
N1 -C10	1.491(16)	C1 -C8	1.569(16)
C2 -C3	1.358(18)	C2 -C7	1.407(16)
C3 -C4	1.388(18)	C4 -C5	1.415(19)
C5 -C6	1.410(19)	C6 -C7	1.349(16)

TABLE 5 Bond angles (°)

C1 -S1 -O1	108.0(6)	C2 -S1 -O1	107.0(6)
C2 -S1 -C1	91.5(5)	C1 -S2 -O2	106.2(5)
C7 -S2 -O2	106.7(6)	C7 -S2 -C1	92.1(5)
C9 -N1 -C8	112(1)	C10 -N1 -C8	110.5(9)
C10 -N1 -C9	112(1)	S2 -C1 -S1	111.1(6)
C8 -C1 -S1	107.6(8)	C8 -C1 -S2	109.2(8)
C3 -C2 -S1	122(1)	C7 -C2 -S1	115(1)
C7 -C2 -C3	121(1)	C4 -C3 -C2	119(1)
C5 -C4 -C3	121(1)	C6 -C5 -C4	118(1)
C7 -C6 -C5	120(1)	C2 -C7 -S2	117.2(9)
C6 -C7 -S2	122(1)	C6 -C7 -C2	120(1)
C1 -C8 -N1	110(1)		

TABLE 6 Intermolecular distances (Å)

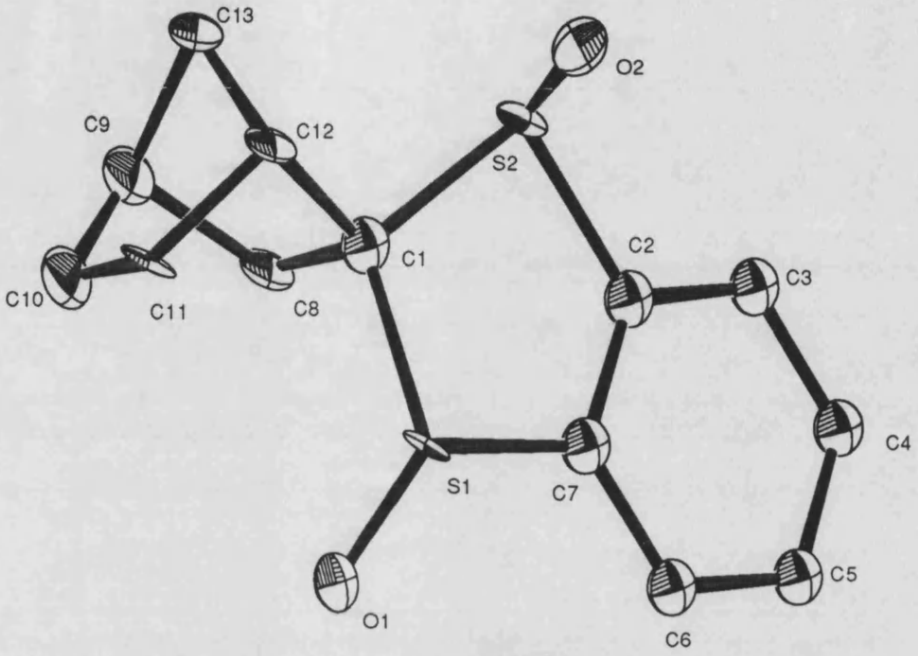
S2	...H92	2.89	1	0.0	1.0	0.0
O1	...H41	2.99	1	1.0	0.0	0.0
O1	...H31	2.35	-1	1.0	0.0	1.0
O1	...H51	2.68	-1	1.0	-1.0	1.0
O1	...H91	2.87	-1	0.0	0.0	1.0
O2	...H103	2.51	1	0.0	1.0	0.0
O2	...H11	2.26	-1	1.0	0.0	2.0
O2	...H93	2.66	-1	0.0	0.0	2.0
O2	...H101	2.61	-1	1.0	0.0	2.0
O2	...H102	2.91	-1	0.0	0.0	2.0
N1	...H61	2.88	1	0.0	-1.0	0.0
C3	...H82	2.58	1	-1.0	0.0	0.0
C4	...H82	2.86	1	-1.0	0.0	0.0

TABLE 7 Intramolecular distances (Å)

S1	...H11	2.43	S1 ...C3 2.79
S1	...H31	2.94	S1 ...C7 2.73
S1	...C8	2.75	S1 ...H82 2.88
S2	...H11	2.40	S2 ...C2 2.74
S2	...C6	2.76	S2 ...H61 2.93
S2	...C8	2.77	S2 ...H81 2.87
S2	...H82	2.99	O1 ...C1 2.68
O1	...C2	2.66	O1 ...C8 2.98
O1	...H82	2.56	O2 ...C1 2.67

O2 ...H11 2.65	O2 ...C7 2.66
N1 ...C1 2.48	N1 ...H11 2.69
N1 ...H81 2.07	N1 ...H82 2.08
N1 ...H91 2.06	N1 ...H92 2.05
N1 ...H93 2.07	N1 ...H101 2.11
N1 ...H102 2.12	N1 ...H103 2.11
C1 ...C2 2.61	C1 ...C7 2.61
C1 ...H81 2.16	C1 ...H82 2.19
C1 ...H101 2.71	H11 ...C8 2.19
H11 ...C10 2.77	C2 ...H31 2.12
C2 ...C4 2.36	C2 ...C5 2.77
C2 ...C6 2.39	C3 ...H41 2.14
C3 ...C5 2.44	C3 ...C6 2.80
C3 ...C7 2.41	H31 ...C4 2.15
C4 ...H51 2.18	C4 ...C6 2.43
C4 ...C7 2.76	H41 ...C5 2.16
C5 ...H61 2.15	C5 ...C7 2.39
H51 ...C6 2.17	H61 ...C7 2.12
C8 ...C9 2.39	C8 ...H91 2.59
C ...H93 2.68	C8 ...C10 2.41
C8 ...H101 2.60	C8 ...H102 2.71
H81 ...C9 2.84	H81 ...C10 2.49
H82 ...C9 2.47	C9 ...C10 2.42
C9 ...H102 2.67	C9 ...H103 2.68
H92 ...C10 2.65	H93 ...C10 2.66

NOTE ON (196).



(196)

A crystal of approximate dimensions 0.3 x 0.3 x 0.25 mm was used for data collection.

Crystal data: $C_{13}H_{12}O_2S_2$, M = 264.4, triclinic, a = 7.908(2), b = 8.146(1), c = 9.730(3)Å, $\underline{\alpha}$ = 73.78(2), $\underline{\beta}$ = 79.31(2), γ = 82.05(2)°, U = 589.5 Å^3, space group $P1$, Z = 2, D_c = 1.50 gcm^{-3}, μ(Mo-K_α) = 3.79 cm^{-1}, F(000) = 2400. Data were measured at room temperature on a Hilger and Watts Y290 four-circle diffractometer in the range $2 \leq \theta \leq 22^\circ$. 1542 reflections were collected of which 1038 were unique with $I \geq 3\sigma(I)$. Data were corrected for Lorentz and polarization effects but not for absorption. The structure was solved by Direct methods and refined using the SHELX[2,3] suite of programs. In the final least squares cycles the sulphur and oxygen atoms along with carbons 8-13 were allowed to vibrate anisotropically. All other atoms were treated isotropically. Hydrogen atoms were included at calculated positions where relevant

except on carbons 9 and 10 where the hydrogen atoms were located in the penultimate difference Fourier and the positions refined with a restricted C - H bond length of 1.08Å in the final convergence map. Final residuals after 12 cycles of least squares were $R = R_w = 0.0889$ for unit weights. Max. final shift/esd was 0.002, the average being 0.001. The max. and min. residual densities were 0.28 and -0.33eÅ^{-3} respectively. Final fractional atomic coordinates and isotropic thermal parameters, bond distances and angles are given in the following tables. Tables of anisotropic temperature factors and hydrogen atom positions are available as supplementary data.

1. Walker N., Stuart D., DIFABS, a program to correct for absorption effects in crystals, Acta Cryst., (1983),A39,158.

2. Sheldrick G.M., SHELX86, a computer program for crystal structure determination, University of Göttingen, 1986.

3. Sheldrick G.M., SHELX76, a computer program for crystal structure determination, University of Cambridge, 1976.

TABLE 1 Fractional atomic coordinates and thermal parameters (Å) for (**196**)

Atom	x	y	z	Uiso or Ueq (***)
S1	0.0963(3)	0.9722(3)	0.6655(4)	0.054(2) ***
S2	0.3070(3)	1.2105(3)	0.7338(4)	0.055(2) ***
O1	-0.0243(10)	0.8452(9)	0.7566(12)	0.067(6) ***
O2	0.4151(8)	1.2581(9)	0.5894(11)	0.056(6) ***
C8	0.4390(12)	0.8783(13)	0.7297(17)	0.054(8) ***
C9	0.3927(14)	0.6951(15)	0.7515(20)	0.058(9) ***
C10	0.3538(15)	0.6308(15)	0.8923(20)	0.058(10) ***
C11	0.3729(14)	0.7637(14)	0.9661(18)	0.060(9) ***
C12	0.2183(13)	0.9035(14)	0.9334(15)	0.053(8) ***
C13	0.5226(13)	0.8558(15)	0.8576(17)	0.059(9) ***
C1	0.2658(12)	0.9840(12)	0.7701(12)	0.034(2)
C2	-0.0049(12)	1.1785(12)	0.6740(12)	0.033(2)
C3	-0.1706(12)	1.2351(12)	0.6368(12)	0.037(2)
C4	-0.2382(13)	1.4003(13)	0.6380(13)	0.043(3)
C5	-0.1441(13)	1.5079(14)	0.6790(14)	0.046(3)
C6	0.0192(13)	1.4528(13)	0.7153(13)	0.045(3)
C7	0.0872(12)	1.2871(12)	0.7094(13)	0.039(3)

TABLE 2 Fractional atomic coordinates for the hydrogen atoms

Atom	x	y	z
H31	-0.2430	1.1504	0.6074
H41	-0.3622	1.4486	0.6040

H51	-0.2006	1.6344	0.6854
H61	0.0914	1.5350	0.7477
H81	0.5088	0.9316	0.6234
H91	0.3929	0.6493	0.6575
H101	0.3069	0.5148	0.9661
H111	0.3855	0.7157	1.0794
H121	0.2100	0.9982	0.9935
H122	0.0974	0.8461	0.9579
H131	0.5389	0.9756	0.8783
H132	0.6439	0.7766	0.8578

TABLE 3 Anisotropic thermal parameters (Å)

Atom	U11	U22	U33	U23	U13	U12
S1	0.038(2)	0.032(1)	0.092(3)	-0.031(2)	-0.025(2)	0.008(1)
S2	0.032(1)	0.033(1)	0.102(3)	-0.021(2)	-0.019(2)	-0.004(1)
O1	0.055(5)	0.028(4)	0.119(9)	-0.003(4)	-0.034(5)	-0.005(3)
O2	0.025(4)	0.053(5)	0.091(8)	0.006(4)	-0.003(4)	-0.012(3)
C8	0.019(5)	0.042(6)	0.100(13)	-0.021(7)	-0.003(6)	0.005(4)
C9	0.031(6)	0.045(7)	0.098(14)	-0.037(8)	-0.009(7)	0.012(5)
C10	0.041(7)	0.040(7)	0.092(15)	-0.010(8)	0.000(7)	0.006(5)
C11	0.040(7)	0.045(7)	0.094(13)	-0.015(7)	-0.003(7)	0.009(5)
C12	0.027(6)	0.045(6)	0.086(12)	-0.024(7)	-0.002(6)	0.002(5)
C13	0.025(6)	0.052(7)	0.102(14)	-0.022(7)	-0.013(6)	0.008(5)

TABLE 4 Bond lengths (Å)

S1 -O1	1.488(9)	S1 -C1	1.854(10)
S1 -C2	1.777(9)	S2 -O2	1.482(10)
S2 -C1	1.844(9)	S2 -C7	1.799(10)
C1 -C8	1.561(13)	C1 -C12	1.536(17)
C2 -C3	1.406(14)	C2 -C7	1.369(14)
C3 -C4	1.381(13)	C4 -C5	1.403(15)
C5 -C6	1.384(15)	C6 -C7	1.396(14)
C8 -C9	1.535(15)	C8 -C13	1.470(19)
C9 -C10	1.317(20)	C10 -C11	1.495(19)
C11 -C12	1.566(15)	C11 -C13	1.556(17)

TABLE 5 Bond angles (°)

C1 -S1 -O1	109.3(5)	C2 -S1 -O1	106.9(5)
C2 -S1 -C1	93.0(4)	C1 -S2 -O2	107.6(5)
C7 -S2 -O2	107.1(5)	C7 -S2 -C1	92.9(4)
S2 -C1 -S1	108.6(5)	C8 -C1 -S1	112.7(8)
C8 -C1 -S2	108.8(7)	C12 -C1 -S1	112.8(7)
C12 -C1 -S2	111.0(7)	C12 -C1 -C8	102.8(9)
C3 -C2 -S1	121.7(7)	C7 -C2 -S1	118.2(7)
C7 -C2 -C3	120.0(9)	C4 -C3 -C2	118.9(9)
C5 -C4 -C3	120(1)	C6 -C5 -C4	121(1)
C7 -C6 -C5	118(1)	C2 -C7 -S2	116.2(7)
C6 -C7 -S2	121.7(8)	C6 -C7 -C2	122.0(9)

C9 -C8 -C1	105.9(8)	C13 -C8 -C1	101(1)
C13 -C8 -C9	101(1)	C10 -C9 -C8	106(1)
C11 -C10 -C9	108(1)	C12 -C11 -C10	105(1)
C13 -C11 -C10	100(1)	C13 -C11 -C12	100(1)
C11 -C12 -C1	102.4(9)	C11 -C13 -C8	94(1)

TABLE 6 Intermolecular distances (Å)

O1 ...H51	2.66	1	0.0	1.0	0.0
O1 ...H61	2.59	1	0.0	1.0	0.0
O1 ...H132	2.70	1	1.0	0.0	0.0
O2 ...H31	2.75	1	-1.0	0.0	0.0
O2 ...H41	2.55	1	-1.0	0.0	0.0
O2 ...H41	2.63	-1	0.0	3.0	1.0
O2 ...H81	2.85	-1	1.0	2.0	1.0
O2 ...H91	2.57	-1	1.0	2.0	1.0
C4 ...H111	2.73	-1	0.0	2.0	2.0
H61 ...C9	2.88	1	0.0	-1.0	0.0

TABLE 7 Intramolecular distances (Å)

S1 ...C3	2.79	S1 ...H31	2.94
C1 ...C7	2.71	S1 ...C8	2.85
S1 ...C12	2.83	S1 ...H122	2.74
S2 ...C2	2.70	S2 ...C6	2.80
S2 ...H61	2.97	S2 ...C8	2.77

S2 ...H81 2.93	S2 ...C12 2.79
S2 ...H121 2.68	S2 ...H131 2.74
O1 ...C1 2.73	O1 ...C2 2.63
O1 ...C12 2.97	O1 ...H122 2.34
O2 ...C1 2.69	O2 ...C7 2.65
O2 ...H81 2.61	C1 ...C2 2.64
C1 ...C7 2.64	C1 ...H81 2.24
C1 ...C9 2.47	C1 ...C10 2.83
C1 ...C11 2.42	C1 ...H121 2.17
C1 ...H122 2.18	C1 ...C13 2.35
C1 ...H131 2.56	C2 ...H31 2.16
C2 ...C4 2.40	C2 ...C5 2.77
C2 ...C6 2.42	C3 ...H41 2.14
C3 ...C5 2.41	C3 ...C6 2.81
C3 ...C7 2.40	H31 ...C4 2.15
C4 ...H51 2.16	C4 ...C6 2.43
C4 ...C7 2.76	H41 ...C5 2.15
C5 ...H61 2.15	C5 ...C7 2.38
H51 ...C6 2.13	H61 ...C7 2.16
C8 ...H91 2.27	C8 ...C10 2.29
C8 ...C11 2.22	C8 ...C12 2.42
C8 ...H131 2.14	C8 ...H132 2.16
H81 ...C9 2.20	H81 ...C13 2.21
C9 ...H101 2.24	C9 ...C11 2.28
C9 ...C12 2.84	C9 ...C13 2.31
C9 ...H132 2.64	H91 ...C10 2.21

APPENDIX TWO

PUBLICATIONS

PUBLICATIONS

(1) V.K. Aggarwal, M. Lightowler and S.D.Lindell.
Trans-dioxides of cyclic ketene thioacetals:
Highly selective chiral ketene equivalents
Synlett., 1992, 730.

trans-Dioxides of Cyclic Ketene Thioacetals: Highly Selective Chiral Ketene Equivalents

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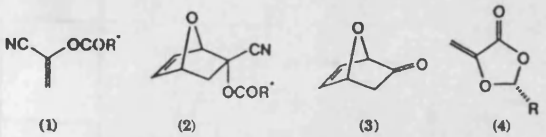
Received 21 May 1992

Abstract: *trans*-2-Methylene-1,3-dithiane 1,3-dioxide (14) and *trans*-2-methylene-1,3-benzodithiolane 1,3-dioxide (11) have been prepared and found to react with dienes, including furan, in a highly diasteroselective fashion. These compounds represent potential chiral ketene equivalents.

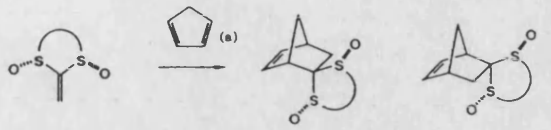
Ketene equivalents have found wide use in synthesis because they readily undergo [4+2] cycloadditions with dienes, whereas ketene itself gives [2+2] cycloadducts. α-Acetoxyacrylonitrile was the first ketene equivalent to be developed[1] and is still used today. Nitroethene[2] and α-chloroacryloyl chloride[3] are also commonly used. With these reagents monocyclic and bicyclic unsaturated ketones have become readily accessible and such compounds have found widespread use as intermediates in organic synthesis.[4]

The current emphasis on homochiral synthesis has prompted investigations into chiral ketene equivalents. Chiral ketene equivalents based upon the condensation product between chiral acid chlorides and pyruvonitrile have been used extensively by Vögel[5] for the synthesis of the enone 3 - an important precursor in the synthesis of biologically active products.[5c] The ketene equivalent 1 gives rise to a mixture of Diels-Alder adducts with furan and whilst the pure enone precursor 2 can be isolated by crystallisation (35% yield) this dienophile would not be appropriate for reactions with more complex and valuable dienes. Those ketene equivalents based on vinyl sulfoxides tend to show low dienophilicity or give rise to complex mixtures of diastereoisomers which are often inseparable and thus limit their synthetic use.[6] Perhaps the most promising chiral ketene equivalent to date is 4 which reacts with a variety of dienes to give Diels-Alder adducts with total face selectivity and good to excellent *exo:endo* selectivity.[7]



(1) (2) (3) (4)

We have returned to ketene equivalents, but based on novel cyclic, alkenyl sulfoxides of general structure 5 since we believe they offer several advantages: (a) the low steric bulk together with the presence of two activating groups at the same carbon should result in high Diels Alder reactivity (b) C_2 symmetry reduces the number of different approaches of the diene and should enhance the selectivity.[8] Since 5 possesses conformationally locked sulfoxides this should further enhance the selectivity.[9] In this communication we describe the synthesis and cycloaddition reactions of the dienophiles 11 and 14. Recently, other workers have also reported on the Diels-Alder chemistry of related cyclic alkenyl sulfoxides.[6e, 6f] However only modest selectivity (3:1) was reported for reactions with cyclopentadiene, whereas 11 and 14 show superior results as shown in Table 1.



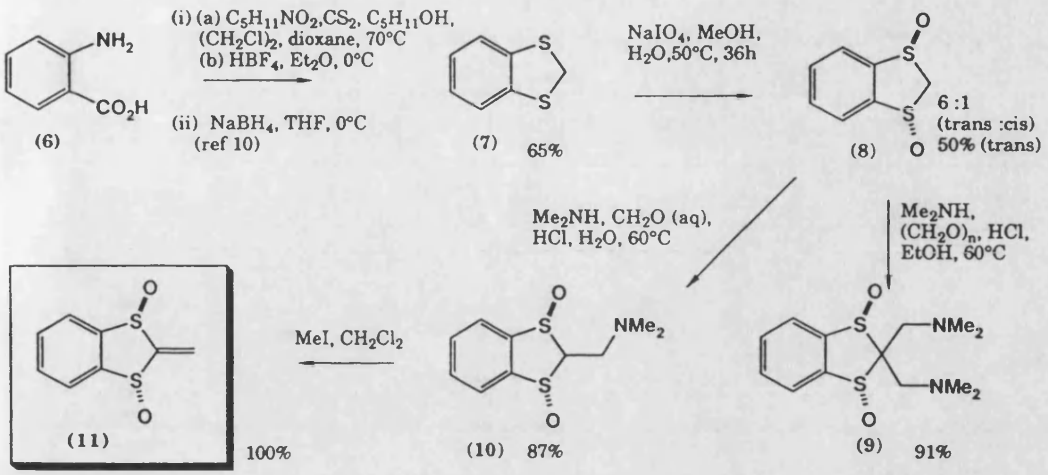
(5) 15a : 15b from 11
19a : 19a from 14

The preparation of **11** is shown in Scheme 1. Benzodithiole 7, prepared from anthranilic acid,[10] was oxidised with $NaIO_4$[11] to give a 6:1 (*trans:cis*) mixture of diastereoisomers which were readily separable. Attempted Mannich reaction[12] carried out in ethanol gave the bis-Mannich adduct **9** in essentially quantitative yield. However, under otherwise identical conditions but *carrying out the reaction in water instead of ethanol gave, exclusively, the desired mono adduct 10*. Treatment with excess MeI gave the alkene **11** directly which was used without further purification.

The dienophile **14** was prepared by metallation of the dioxide **12**,[11,13] quenching with monomeric formaldehyde[14] followed by elimination using the water soluble DCC variant (morpho CDI) and catalytic $CuCl_2$[15] (Scheme 2).

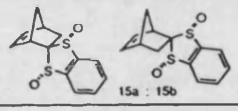
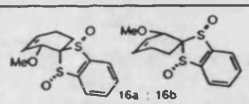
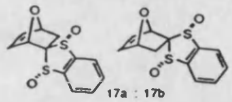
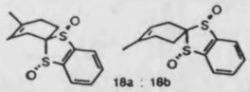
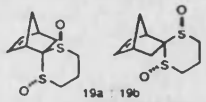
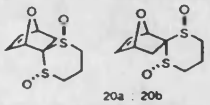
The results of Diels Alder reactions between a variety of dienes and the dienophiles **11** and **14** are summarised in Table 1. It was found that both the rate and selectivity of the reaction between cyclopentadiene and **11** increased with solvents of increasing polarity.[16] The highest selectivity for reaction with cyclopentadiene was found with $BF_3.OEt_2$ catalysis at -78°C giving a 15:1 ratio of diastereoisomers. A single recrystallisation gave diastereomerically pure **15a** whose structure was proved by X-ray crystallography.[17] Acyclic dienes reacted even more selectively (entry 2) and even in the absence of Lewis acids only the single adduct **16a** was observed. Even furan, a much poorer diene compared to the others, reacted with good stereocontrol with dienophile **11** (entry 3) though in this case best results were obtained with $SnCl_4$. Reactions with the dithiane based dienophile **14** were also carried out and again the results are summarised in Table 1. In contrast to **11**, **14** furnished *a single diastereoisomer with cyclopentadiene* but showed poorer selectivity with furan. Both **11** and **14** showed low levels of selectivity with furan under $BF_3.OEt_2$ catalysis (both ~ 1.8:1) but while improved selectivity was obtained for dienophile **11** using $SnCl_4$, similar use of $SnCl_4$ with dienophile **14** resulted in decomposition. Failure of **14** to react with 1-substituted acyclic dienes (entry 6) is probably the result of unfavourable steric interactions of the diene substituent with axial groups of the dithiane moiety. There are no such axial groups on dienophile **11** to interact with the diene thereby allowing such reactions to occur.

The preferred formation of **15a** over **15b** (and **19a** over **19b**) results from **TS1** being favoured over **TS2**. **TS2** suffers from greater non-



Scheme 1

Table 1. Diels Alder Reactions Between Dienophiles 11 & 14 with Various Dienes

entry	diene	dienophile	Lewis acid	temp. (°C)/ time	Diels-Alder adducts	ratio of adducts (a:b)	yield
1	cyclopentadiene	11	BF_3OEt_2	-78 5 min	 15a : 15b	15:1	75%[b]
2	1-methoxy-butadiene	11	-	RT 24 h	 16a : 16b	> 25:1	78%[b]
3	furan	11	$SnCl_4$	-78 30 min	 17a : 17b	5:1[c]	98%[b]
4	isoprene	11	-	RT 6 h	 18a : 18b	12:1[d]	70%[b]
5	cyclopentadiene	14	BF_3OEt_2	-78 10 min	 19a : 19b	> 25:1	80%
6	1-methoxy-butadiene	14	-	RT	no reaction	-	-
7	furan	14	BF_3OEt_2[e]	-78 1 h	 20a : 20b	1.8:1	95%

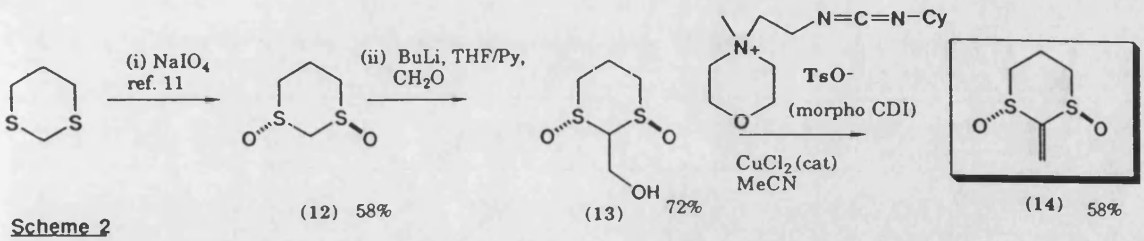
a Ratios were determined by NMR integration of the crude reaction mixture.

b Yield based on amine 10.

c Kinetic ratio. Subjection of the minor diastereoisomer to the same reaction conditions left it unchanged.

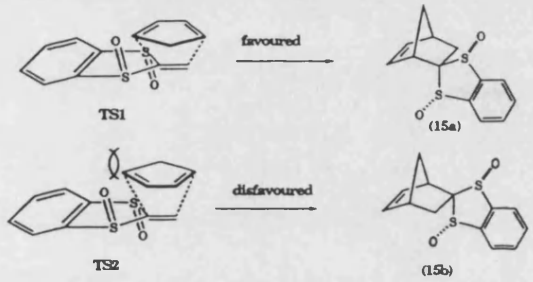
d CF_3CH_2OH was used as solvent.

e Use of $SnCl_4$ or other Lewis acids either gave no reaction or lead to decomposition.



Scheme 2

bonded interactions than TS1 between the sulfinyl oxygen and the diene substituent. Lewis acids serve not only to increase the reactivity of the dienophile but the effect of binding to the sulfinyl oxygen results in an increase in its effective size thereby increasing the steric interactions involved in TS2. Hence, high selectivities are seen in Diels-Alder reactions promoted by Lewis acids.



These results suggest that the dithiolane based dienophile **11** is in general more reactive and more selective than the dithiane based dienophile **14**. We are currently in the process of investigating further modifications of cyclic alkenyl sulfoxides of general structure **5** as a means of further improving the diastereoselectivity of the cycloaddition process.

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References and Notes

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1 Bartlett, P.D.; Tate, B.E. *J. Am. Chem. Soc.*, 1956, *78*, 2473.

2 McMurray, J.E.; Melton, J. *J. Org. Chem.* , 1973, *38*, 4367. Ranganathan, S.; Ranganathan,D.; Mehrotra, A.K. *J. Am. Chem. Soc.*, 1974, *96*, 5261.

3 Corey, E.J.; Ravindranathan, T.; Terashima, S. *J. Am. Chem. Soc.*, 1971, *93*, 4326.

4 For applications of ketene equivalents to the synthesis of (a) prostaglandins see ref 3 (b) reserpine see Baxter, E.; Labaree, D.; Chao, S.; Mariano, P.S. *J. Org. Chem.*, 1989, *54*, 2893. Wender, P.A.; Schaus, J.M.; White, A.W. *J. Am. Chem. Soc.*, 1980, *102*, 6159. (c) antibiotics see Hori, K.; Nomura,K.; Mori, S.; Yoshii, E. *J. Chem. Soc., Chem. Commun.*, 1989, 712. For a review see Ranganathan, S.; Ranganathan,D.; Mehrotra, A.K. *Synthesis*, 1977, 289.

5 (a) Viera, E.; Vogel, P. *Helvetica Chimica. Acta*, 1983, *66*, 1865. (b) Reymond, J.L.; Vogel, P. *J. Chem. Soc., Chem. Commun.*, 1990, 1070. (c) Vogel, P.; Fattori, D.; Gasparini, F.; Le Drian, C. *Synlett*, 1990, 173. (d) Reymond, J.L.; Vogel, P. *Tetrahedron Asymm.*, 1990, *1*, 729.

6 (a) Maignan, C.; Raphael, R.A.; *Tetrahedron*, 1983, *39*, 3245; (b) Arai, Y.; Kuwayama, S.; Takeuchi, Y.; Koizumi, T. *Synth. Commun.*, 1986, 233. (c) Williams, R.V.; Lin, X. *J. Chem. Soc., Chem. Commun.*, 1989, 1872. (d) Katagiri, N.; Ise, S.; Watanabe, N.; Kaneko, C. *Chem. Pharm. Bull.*, 1990, *38*, 3242. (e) De Lucci, O.; Fabbri, D.; Lucchini, V. *Synlett*, 1991, 565. (f) Lopez, R.; Carretero, J.C. *Tetrahedron Asymm.*, 1991, *2*, 93. For a review see De Lucchi, O.; Pasquato, L. *Tetrahedron*, 1988, *44*, 6755.

7 (a) Mattay, J.; Mertes, J.; Maas, G. *Chem. Ber..*, 1989, *122*, 327. (b) Roush, W.R.; Essenfeld, A.P.; Warmus, J.S.; Brown, B.B. *Tetrahedron Lett.*, 1989, *30*, 7305.

8 (a) Najdi, S.; Kurth, M.J.; *Tetrahedron Lett.* 1990, *31*, 3279. (b) Whitesell, J.K. *Chem. Rev.* 1989, *89*, 1581.

9 A dienophile with a conformationally locked sulfoxide giving good stereocontrol has been reported: Waldner, A. *Tetradedron Lett.*, 1989, *30*, 3061.

10 (a) Nakayama, J. *Synthesis*, 1975, 436. (b) Nakayama, J.; Fujiwara, K.; Hoshino, M.; *Bull. Chem. Soc. Jap.*, 1976, *49*, 3567. (c) For a review see Nakayama, J. *Sulphur Reports*, 1985, *4*, 159.

11 Aggarwal, V.K.; Davies, I.W.; Franklin, R.J.; Maddock, J.; Mahon, M.F.; Molloy, K.C. *J. Chem. Soc., Perkin. Trans 1*, 1991, 662.

12 For a review on the Mannich reaction see: Tramontini, M.; Angiolini, L. *Tetrahedron*, 1990, *46*, 1791.

13 Aggarwal, V.K.; Davies, I.W.; Maddock, J.; Mahon, M.F.; Molloy, K.C. *Tetrahedron Lett..*, 1990, *31*, 135. Aggarwal, V.K.; Franklin, R.J.; Rice, M.J. *ibid*, 1991, *32*, 7743.

14 Schlosser, M. Jenny, T.; Guggisberg, Y. *Synlett*, 1990, 704.

15 Andrews, R.C.; Marshall, J.A.; DeHoff, B.S. *Syn. Commun.*, 1986, *16*, 1593.

16 Details of the solvent effects will be described in the full paper.

17 It is assumed that the major distereoisomers formed in the other reactions have the same relative stereochemistry as **15a**.